Painless childbirth? Epidural and spinal techniques in obstetric anesthesia

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Chapter 1

Introduction

1. INTRODUCTION TO OBSTETRIC ANESTHESIA

Were it not for Queen Victoria and her singular authority to challenge and silence medical, religious and political opposition in the UK in the 1850's, the initial development of obstetric anesthesia would have missed a crucial momentum. In an era where women's voices were seldom heard, her sardonic "Then let the bishops have the babies Mr. Gladstone" could not be ignored.(1)

Fig. 1. Queen Victoria with her daughter Victoria, the princess Royal.

(By Henry Collen: public domain, via Wikimedia Commons)

The evolution of obstetric anesthesia is closely aligned with the emergence and development of modern-day anesthesia in general, but obstetric anesthesia involves much more than a mere adaptation of standard anesthetic practices. The profound (patho)physiological transformations of pregnancy, the complex needs of women and their unborn children, the unpredictable challenges that may arise, and the need for crucial immediate anesthetic services demand a thorough understanding of fetal-maternal physiology, pathology and obstetric procedures.

Pregnancy and childbirth are fundamentally natural but complex physiological processes which unfortunately have historically been accompanied by significant feto-maternal morbidity and mortality. The advances in modern healthcare, including obstetric anesthesia, have dramatically reduced these risks. For many women, labour and delivery unfold as nature intended, but the delicate interplay between the physiology of labour, maternal coping capacity, and available support may not always suffice. When medical intervention becomes necessary, whether for pain relief, an urgent cesarean delivery, or surgery to address obstetric complications. anesthesia plays a crucial role.

This specialized field requires a combination of technical expertise, knowledge of administration tools and medications, understanding of maternal-fetal medicine, and strong interpersonal skills. Together with timely maternal education on pain relief options and potential anesthetic strategies during unexpected emergencies this also promotes clear communication and respects maternal autonomy, ultimately improving shared decision-making and well-being during childbirth and beyond.

Evolution of obstetric anesthesia

The evolution of obstetric anesthesia is closely aligned with the emergence and development of modern-day anesthesia in general. Within months after the first public use of ether for a surgical intervention in 1846, ether and soon thereafter chloroform were utilized to relieve the suffering of labour during childbirth and facilitate complicated deliveries in various European countries, including the Netherlands (1).

The use of inhalational analgesia during labour gradually spread, especially in the Anglo-Saxon countries. Elsewhere, a more cautious approach to the use of anesthesia and analgesia in obstetrics persisted, but as the anesthetic toolbox steadily expanded with new drugs and administration tools, the advantages of anesthesia in painful, complicated, or obstructed labours could no longer be dismissed.

New inhalational agents, intravenous anaesthetic drugs, and tools to ventilate patients while under anesthesia were introduced, which increased the use and gradually also the safety of general anesthesia. All these techniques soon found their way to obstetrics, for anesthesia during surgical procedures or to provide analgesia during labour. Together with the introduction of strict antisepsis measures, they led to new surgical delivery techniques and improved outcomes for cases previously requiring destructive procedures like craniotomy (where the fetus was extracted in pieces to save the mother's life).

These advances had initially paradoxical effects on maternal outcomes. Caesarean delivery previously considered a hazardous with pre-antisepsis mortality rates as high as 70-100%, indeed became safer.(2) Unfortunately, increased provision of labour analgesia, while reducing the pain associated with labour and delivery, also facilitated medicalisation of childbirth with

unexpected negative consequences. Inexperienced administration of inhalational analgesia, lack of understanding of the working mechanisms, presence of undesirable side-effects, and absence of adequate monitoring all contributed to elevated hazards.(3) In the USA, its widespread adoption also led to an increased incidence of forceps deliveries, as women under heavy sedation were unable to push effectively. This resulted in an higher incidence of maternal complications and deaths compared to countries that maintained a more natural approach to labour and delivery.(4)

The origins of neuraxial techniques

The introduction of neuraxial techniques marked a revolutionary development in anesthesia. It was the surgeon August Bier who first injected cocaine in the lumbar intrathecal space in order to achieve anesthesia of the lower body. In 1898 he performed the first 6 successful cases of spinal anesthesia as the technique became known. Although 3 out of 6 cases also resulted in a severe positional headache which lasted several days, spinal anesthesia appeared a promising alternative to inhalational anesthesia.(3,5) Initially the technique gained popularity, and within 2 years Oskar Kreis used spinal anesthesia to relieve labour pain.(3) Although Bier soon abandoned the technique, due to concerns over complications, addiction potential and toxicity of cocaine, spinal anesthesia became widely used once a safer local anesthetic (LA), procaine, was developed in 1904, which effectively replaced cocaine.(6) But spinal anesthesia remained a dangerous technique with a high risk of cardiovascular and respiratory depression and compromise. When administered by inexperienced personnel without adequate monitoring, it resulted in mortality rates as high as 1 in 139 among pregnant women, as reported in Germany in 1934.(3) The beforementioned risks soon led to the search for alternative L.A. administration routes. Pudendal, paravertebral sacral and caudal epidural routes were all explored and developed in the years that followed. Eventually the lumbar epidural approach was used in labour, first described around 1938 by early pioneers like Pagés and Dogliotti.(6). Since then, epidural anesthesia has developed as an alternative to general anesthesia, which at that time carried inherent risks, such as failed airway management, aspiration and neonatal compromise due to transplacental transfer of anesthetics. The subsequent refinements in epidural analgesia -including reduced LA concentrations, addition of synergistic opioids- and improvements in spinal needle design have established neuraxial (epidural and spinal) procedures as the cornerstone of obstetric anesthesia.

2. PAIN IN OBSTETRICS

Pregnancy and childbirth are inevitably linked with a certain degree of discomfort and suffering, sometimes even resulting in a physical ordeal which can extend well beyond delivery. Mechanical factors such as stretching of supportive abdominal ligaments, postural changes due to the increasing weight of the gravid uterus, and increased laxity of the sacro-iliac joints resulting from hormonal changes, all contribute to musculoskeletal discomfort during pregnancy. Both vaginal and operative deliveries invariably cause acute tissue injury,

which not only further increases acute visceral pain during vaginal delivery, but may also lead to central sensitization, scar tissue and chronic postsurgical pain. Together with a changed pelvic architecture, which may never regain its original stability, it leaves a significant minority of women with unresolved and long-lasting discomfort.

Labour pain

Multiple areas of the central nervous system interact dynamically to generate individualized pain experiences during childbirth. Nociceptive input from the lower uterine segment, cervix and vagina travels through the thalamus to the somatosensory cortex. Individual pain perception varies due to suprathalamic modulation, which is influenced by neurohormonal processes, autonomic nervous system balance, previous experiences, sociocultural beliefs/ expectations, available support and maternal emotional state.(7,8).

During the first stage of labour, uterine contractions result in stretching of the lower uterine segment and cervical dilation, activating visceral afferent nerve fibers with thoracolumbar origins. This produces diffuse dull, visceral-like pain that characteristically waxes and wanes with the rhythm of contractions. Once the fetus descends further during the second stage, additional nociceptive input from pelvic floor tissue injury travels through sacral A-delta fibers, creating more localized, intense pain sensations.

The severity of labour pain varies significantly among women due to mechanical factors (cephalopelvic disproportion, fetal presentation, contraction intensity, obstetric interventions), pre-existing pain conditions, coping mechanisms, psychological state, provided analgesia and quality of care. Research has demonstrated its potential extreme intensity. Melzack quantified it as comparable to the unanesthesized amputation of a finger, while earlier experiments showed that women reproducing their labour pain with heat stimuli ended up with second-degree burns.(8)

Currently clinicians rely on subjective self-reported measurements like the Visual Analogue Scale (VAS) or the numerical rating scale (NRS). (8) While more objective assessment tools based on autonomic responses and neuroimaging are being developed, their application in obstetrics remains challenging due to the fluctuating nature of labour pain.

Pain during and after obstetric surgery

Neuraxial anesthesia for obstetric surgical procedures is achieved either through using an already present and functioning epidural catheter or through spinal anesthesia. Yet anesthesia is not always complete, as during cesarean delivery an uncomfortable pain or pressure may be present or develops which necessitates additional supplemental anesthesia. Incidences of intra-operative breakthrough pain between 1-20% have been reported, irrespective of the neuraxial administration route.(9)

Failure to extend intrapartum epidural analgesia to surgical anesthesia is associated with a previously suboptimal epidural analgesia, suboptimal dosing of LA for epidural anesthesia, degree of urgency of the cesarean delivery, duration of surgery and patient-related risk factors such as high BMI, co-morbidities, younger age and increased height of the patient.(9) After spinal anesthesia, breakthrough pain can occur with prolonged duration of the surgical procedure, inadequate assessment of proper block height before commencement of surgery, and absence of opioids in the intrathecal mixture together with patient related factors. Apart from serious physical and emotional trauma for the mother during operative delivery, breakthrough pain may contribute to persistent pain after childbirth, development of a posttraumatic stress disorder and postpartum depression.(8,10)

Severe postoperative pain is also not uncommon, as cesarean delivery has been determined to be one of the most painful surgical procedures.(11) Inadequate postoperative pain relief not only affects early maternal mobilisation, maternal-neonatal bonding and breastfeeding. It also contributes to development of chronic postsurgical pain: pain associated with the procedure which may last months after the procedure.(12) The severity of acute postpartum pain, both after cesarean and vaginal delivery, has been shown to be associated with persistent pain and postpartum depression at 8 weeks postpartum.(12,13) Both persisting pain and developing depression have negative consequences for maternal, neonatal and family health and wellbeing.

3. NEURAXIAL NEURAL BLOCKADE

Neural blockade results from the interaction of local anesthetics with various ion channels and receptors of neural cell membranes. Depending on location, dose, volume and concentration of the LA, and the specific characteristics of the nerve fibres, (myelination, diameter and conduction velocity), action potential generation is blocked, conductance along axons is disrupted and release of neurotransmitters and neuropeptides at presynaptic terminals is inhibited.(14)

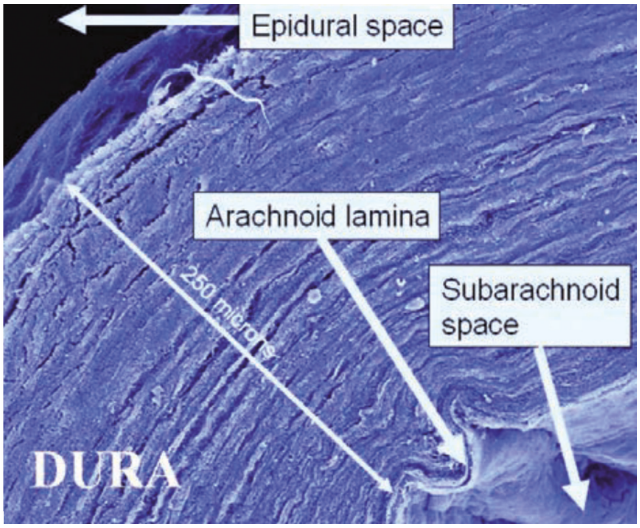
To achieve neural blockade in the neuraxial space, local anaesthetics are administered either in the intrathecal (subarachnoid) space or in the epidural space, targeting spinal cord tissue or spinal nerve roots and the dorsal root ganglia. Addition of opioids provides a synergistic effect through different receptor mechanisms, resulting in more profound anesthesia. For labour analgesia, where pain reduction rather than complete sensory loss is the aim, this combination facilitates reduction of LA concentration. This approach achieves targeted analgesia instead of profound anesthesia, which is desirable for labour as it preserves motor function and minimizes undesirable side effects such as motor block, sympathetic blockade (potentially causing hypotension), urinary retention and complete sensory loss that might interfere with pushing during the second stage.

Anatomy and physiology of the neuraxial space

The spinal cord, located within the bony vertebral column, contains a variety of ascending and descending pathways facilitating neural transmission between periphery and brain. Spinal nerves exiting through intervertebral foramina contain sensory fibers, motor fibers and depending on location, sympathetic (T1-L2) or parasympathetic (S2-S4) preganglionic fibers- all potential targets during neuraxial anesthesia.

The spinal cord is surrounded by cerebrospinal fluid (CSF) and three meningeal layers. The outermost dura mater consists of 70-80 permeable sheaths of randomly distributed collagen and fibrinogen fibres through which fluids can diffuse.(15,16)

Fig. 2. The spinal meningeal layers



Scanning electron microscopy image of the meninges showing the concentric rings formed by the dural laminae. (Magnification ×300.)(17)

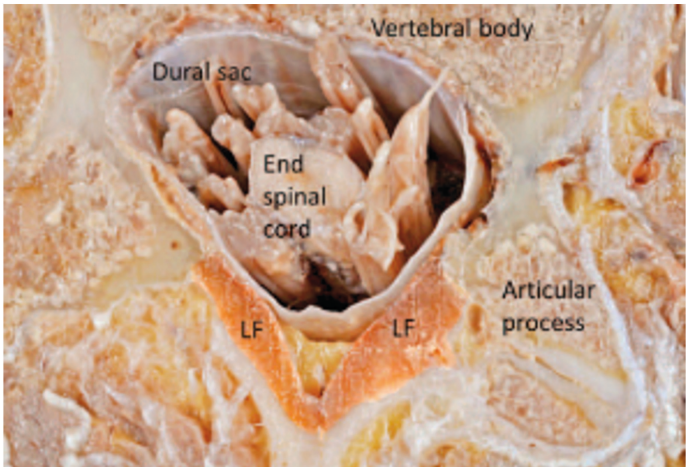
The middle meningeal layer, the arachnoid mater, forms the primary barrier preventing intrathecal CSF from leaking to the surrounding epidural space.(18–21) It is closely aligned with the inner dural surface. (17,22,23) The innermost pia mater adheres directly to the spinal cord.(20)

The subarachnoid space contains cerebrospinal fluid (CSF), which provides hydromechanical protection and maintains CNS homeostasis through a complex dynamic exchange of fluids and substances between CSF, interstitial fluid, nervous tissue and blood.(22,23)

Additional protection of the spinal cord is provided by the epidural compartment, which is far more complexly organized than previously thought and contains compartmentalized fat pads, vessels and fibrous septa.(24,25) The outer limit of the epidural space, the peridural membrane (PDM), encapsulates all components within the spinal canal including nerves, arteries, lymphatics and the epidural venous plexus.(26,27)

During neuraxial procedures, the ligamentum flavum – a supportive ligament connecting vertebral laminae posteriorly- must be passed. In epidural procedures, when one intends to stay outside the dural sac, it facilitates identification of the epidural compartment. When inserting an epidural needle with a saline or air-filled syringe attached upon which constant pressure is applied, the resistance the ligamentum flavum provides suddenly diminishes upon needle entry in the epidural compartment (loss of resistance technique). As the flavum is a paired structure with variable midline fusion, identification of the epidural space is not always straightforward, potentially leading to accidental dural puncture (Fig.3).(28)

Fig. 3 Transverse section of the human lumbar spine at L1 vertebral level.(28)



Abbreviation: LF, ligamentum flavum.

Neuraxial techniques

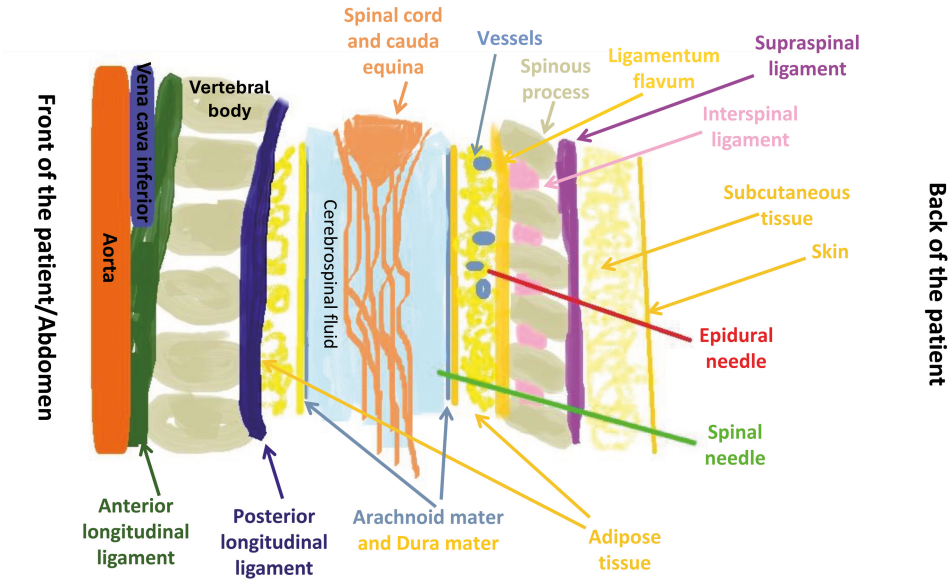
In obstetrics, neuraxial administration of LA, which blocks sensory nerve transmission, is preferred over inhalational or intravenous techniques to provide analgesia and anesthesia. Spinal or epidural drug administration less likely result in plasma concentrations sufficiently high to impact the fetus in utero. Advances in initiation techniques, delivery modes, drug combinations, and monitoring protocols have optimized efficacy and safety while minimizing interference with maternal and fetal wellbeing.

There is an interpatient variable response to neuraxial blockade which can be explained by an array of personal differences in anatomy of the spinal canal, nerve root organisation, CSF movement, epidural fat and vasculature, and co-morbidities which might affect ion channel composition and function. Together with the physiochemical properties and pharmacological actions of the used drug combination, these determine the resulting therapeutic effects and potential complications.

The resulting sensory, motor and sympathetic blockade depends on the injection site, the extent of the exposed nervous tissue surface and the dose and concentration of LA administered. Nerve fiber characteristics such as size, type and myelination also determine the response and extent of nerve blockade. Differences in block height and onset speed are observed between the various nerve fibre types, especially during spinal anesthesia.

Spinal and epidural techniques differ fundamentally in their anatomic target and resulting effects. Spinal anesthesia involves direct injection of local anesthetics into the CSF in the subarachnoid space, providing immediate access to the spinal cord and nerve roots. This results in a rapid onset of anesthesia (3-5 minutes), with a profound block achieved with smaller doses and a predictable duration (1.5-3 hours), depending on LA choice and additives. It is limited to levels below L2/L3 to avoid spinal cord injury, is generally easier to perform technically, has a lower failure rate, but is associated with a more profound and rapid-onset hypotension. As it is a single shot technique, its duration cannot be extended.

Fig. 4. Needle pathways in epidural and spinal techniques (posterior to anterior)



(Courtesy of Dr. Aleksandra Polen)

Epidural anesthesia results from LA injected into the epidural space, outside the dura mater. It requires a larger volume and results in a slower onset (15-20 minutes), as the spread is less predictable due to the more compartmentalized anatomy.(24,29)

The LA act on nerve tissue within the epidural compartment and eventually on intrathecal neural tissue, once diffusion through the meningeal membranes occurs. Contrary to common belief, the main barrier resisting diffusion is not the dural mater but the arachnoid mater. As drugs must pass the aqueous-lipid interface of the 6-8 layers of arachnoid membrane, an intermediate value of lipid solubility is preferable, as compounds with either low or high lipid solubility experience slower spinal diffusion.(16,30)

Table 1 Comparison of the epidural and spinal technique

Feature	Epidural technique	Spinal technique
Anatomical Space	Epidural compartment	Intrathecal space
Spinal level	Possible at all spinal levels, for obstetrics L2/L3 to L4/L5	Below L2/L3
Identification of location	Loss of resistance, hanging drop technique	Changed feeling, popping sensation
Needle Size	Larger (16-18G), facilitating catheter placement	Smaller (25-27G)
Catheter	Yes, can be left in place	No, single-shot technique
Duration	Can be extended with catheter for days	Limited (2-4 hours)
Onset Time	Slower (10-20 minutes)	Rapid (5-10 minutes)
Drug Volume	Larger volumes (10-20 mL)	Small volumes (1.5-3.5 mL)
Drug Concentration	Depending on purpose: anesthesia or analgesia	Depending on purpose, anesthesia or analgesia
Block Height Control	More controllable, gradual spread	Less controllable, rapid spread
Motor Block	Variable/can be minimized	Dense
Risk of PDPH	<1%, in case of accidental dural puncture (ADP)	Needle dependent, currently est. 1%
Hypotension	Less severe, gradual onset	More profound, rapid onset
Ideal Use Cases	Labour analgesia, postoperative pain, prolonged procedures	Cesarean delivery, in CSE also for labour analgesia
Technical Difficulty	More challenging	Relatively easier
Contraindications	Coagulopathy, infection at site, increased ICP	Same as epidural plus hypovolemia
Failure Rate	Higher (10-15%)	Lower (5%)
Post-procedural Care	May require more monitoring due to catheter	Less monitoring if uncomplicated

The difference between anesthesia and analgesia after neuraxial administration lies primarily in the concentration of LA used. Neuraxial (spinal or epidural) anesthesia requires high LA concentrations (such as bupivacaine 0.5% or lidocaine 2%) to achieve complete sensory and motor blockade for surgical procedures. This results in complete sensory and motor block with patient immobility, with more pronounced hemodynamic effects. In contrast, neuraxial analgesia can be achieved with lower concentrated LA solutions (such as bupivacaine 0.0635-0.125% or ropivacaine 0.1-0.2%), often combined with opioids to enhance pain relief while reducing LA requirements. This creates a partial sensory block which provides analgesia with minimal or no motor block, may allow for ambulation with low-concentrated solutions, causes less hemodynamic instability and permits active patient participation (table 2). It can be delivered epidurally via a catheter, facilitating continuous infusion or intermittent boluses, making it ideal for labour pain management.

Table 2 Comparison of Neuraxial Anesthesia and Analgesia

Feature	Neuraxial Anesthesia	Neuraxial Analgesia
Primary Purpose	Complete sensory and motor block for surgical procedures	Pain relief while maintaining some sensory and motor function
Drug Concentration	Higher concentration of local anesthetics	Lower concentration of local anesthetics, often with opioids
Degree of Block	Dense sensory block, complete motor block	Partial sensory block, minimal to no motor block
Patient Mobility	Immobile during effect	May allow ambulation when low concetrated LA solutions are used
Duration of Application	Usually for the duration of surgery	Can be maintained for hours to days (with catheter)
Hemodynamic Effects	More pronounced hypotension and bradycardia	Less hemodynamic instability
Common Applications	Cesarean delivery, lower abdominal/limb surgery	Labour pain, postoperative pain management
Consciousness	Patient remains awake (unless combined with sedation)	Patient remains awake and alert
Method of Administration	Bolus dose(s)	Continuous infusion, intermittent manual or programmed bolus administration
Common Agents	Bupivacaine 0.5%, lidocaine 2%, tetracaine	Bupivacaine 0.0625-0.125%, ropivacaine 0.1-0.2% to which fentanyl or sufentanil is added.
Monitoring Requirements	Continuous vital signs, block level assessment	Intermittent monitoring, regular pain assessment
Patient Participation	Limited during procedure	Active participation possible (e.g., pushing during labour)
Supplementation Needs	Rarely needs supplemental analgesia during procedure	May require additional analgesia in case of breakthrough pain

CONCLUSION

Neuraxial techniques have revolutionized obstetric anesthesia in various ways. They allow effective pain relief during labour when desired, without affecting maternal cognition and awareness, and provide safer anesthesia during caesarean delivery, while allowing women to experience and be present during the birth of their child. Despite continuous refinement of the techniques over decades, the delicate balancing act to provide optimal effectivity while minimizing side-effects and complications continues, as various persistent questions remain unanswered, some if which will be addressed in the studies included in this thesis, which explores these challenges and controversies from various perspectives, addressing several key questions:

As the persistent association between oxytocin augmentation and epidural labour analgesia has not completely been clarified yet, does electrohysterography provide a new tool to study the presence or absence of uterine responses to epidural analgesia initiation (Chapter 2)?

Can neuraxial administered drugs such as intrathecal morphine contribute to a reduced incidence of chronic postsurgical pain (CPSP) following caesarean delivery, and is there an association between CPSP and postpartum depression (chapter 3 and 4)?

Which technique and patient-related factors influence the incidence of hypotension after spinal anesthesia (chapter 5 and 6).

What are the current insights in postdural puncture headache, and what are European perspectives on management practice of PDPH after accidental dural puncture (ADP) during epidural labour analgesia initiation (chapters 7 and 8)? Which factors are associated with success or failure of an epidural blood patch as therapy in these patients, and will new insights in CSF physiology contribute to improved therapeutic options (chapters 9- 10)?

The evidence in these studies provides new insights in the nuances of neuraxial techniques and resulting desired or undesirable consequences. It identifies knowledge gaps and acknowledges that a renewed interest in underlying basic pathophysiologic mechanisms is needed if we want to move forward and further.

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Chapter 2

Uterine contraction frequency after initiation of labour epidural analgesia using electrohysterography monitoring: a prospective pilot study

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ABSTRACT

Background

The introduction of electrohysterography into clinical practice provides new opportunities to study the impact of labour epidural analgesia on uterine contractility because electrohysterography has a greater sensitivity in detecting uterine contractions than external tocodynamometry. We determined the uterine contraction frequency before and after initiation of labour epidural analgesia using an electrohysterography-derived tocogram.

Methods

This prospective study included 23 pregnant women between 36-42 weeks' gestation with a singleton cephalic presentation who requested epidural analgesia in active labour. The primary study outcome was the difference in mean uterine contraction frequency 60 minutes before and 120 minutes after epidural analgesia initiation. The secondary aim was to measure changes in mean contraction frequency over time, using the mean uterine contraction frequency per 10 minutes, derived from 30-minute averages.

Results

In the 120 minutes after epidural analgesia initiation, the average contraction frequency decreased significantly (-0.37 contractions/10 minutes [95% CI -0.64 to -0.11]; P = 0.007) compared to the 60 minutes before epidural analgesia initiation. The largest decrease occurred 60-90 minutes after epidural analgesia initiation (-0.47 contractions/10 minutes [95% CI -0.89 to -0.05]; P = 0.029).

Conclusion

During active labour, electrohysterography identified a statistically significant, although clinically small, reduction in uterine contraction frequency after epidural analgesia initiation. This pilot study demonstrates the potential value of electrohysterography monitoring for obstetric anaesthesia research and might renew interest in the still poorly understood interaction between labour epidural analgesia and uterine activity.

INTRODUCTION

Neuraxial labour analgesia is considered the gold standard for pain relief during labour. It provides optimal analgesia with minimal side effects and results in higher maternal comfort and satisfaction compared to other techniques.[1] The effects of labour epidural analgesia (LEA) on uterine activity and contraction frequency are difficult to determine, and therefore are poorly understood.

Surrogate markers of uterine contractility are often used. In the past, increased rates of operative vaginal delivery were reported with LEA use, as well as more frequent use of oxytocin augmentation, and prolonged duration of first and second stage of labour. The use of contemporary solutions of low-concentration local anaesthetics and opioids has mitigated most of these effects, but an increased incidence of oxytocin augmentation persists, although a causal relationship has never been determined.[1]

When measuring uterine activity immediately after LEA initiation, reports of decreased, unchanged, and enhanced uterine activity have been described.[2-4] These conflicting observations may be explained by the wide variety of clinical settings and epidural medication administered as well as different methods used to evaluate uterine activity. These methods include manual palpation, external tocodynamometry, and intrauterine pressure catheter (IUPC).[2]

In current obstetric practice, external tocodynamometry is most commonly used—a non-invasive and easy-to-apply uterine monitoring method. However, the quality is affected by maternal body mass index and maternal and fetal movements, with a poor intra- and interobserver agreement.[5-6] The IUPC provides a more precise measurement of uterine activity, but it is an invasive technique associated with potentially serious complications such as uterine or placental perforation.[7] Since IUPC use does not significantly improve perinatal outcomes, routine use is not recommended.[8]

Electrohysterography has recently become clinically available as a noninvasive monitoring technique; it is more accurate and reliable compared to external tocodynamometry. [9] Electrohysterography measures the electrical myometrial activity, and the resulting parameters can be converted into immediately interpretable waveforms, comparable to intrauterine pressure curves.[5,9-12] It has been shown to have a higher sensitivity for detecting uterine contractions than external tocodynamometry.[2,9,13]

The use of electrohysterography provides an opportunity to improve our understanding of the relationship between epidural analgesia initiation and uterine activity.[14] The primary aim of this pilot study was to use a real-time electrohysterography-derived tocogram to identify potential differences in the mean contraction frequency 60 minutes prior to and 120 minutes following LEA initiation. We hypothesized that no significant change in uterine contraction

frequency would be measurable. Our secondary aim was to measure potential changes in mean contraction frequency over time during the study observation period.

METHODS

This pilot study was part of a prospective observational study on the implementation of non-invasive electrophysiological monitoring during labour in a tertiary care teaching hospital in the Netherlands, which was performed from March 2021 to July 2021.[14] Institutional ethical approval and oral and written informed consent were obtained from healthy pregnant women between 36 and 42 weeks' gestation, with a singleton cephalic fetus with no fetal cardiac arrhythmias and with an indication for continuous intrapartum monitoring. Exclusion criteria were contraindication for the use of the electrohysterography-monitoring device (presence of external or implanted electro-neurostimulators, pacemakers, maternal abdominal dermatologic disease, water-birthing), contraindication for the use of a fetal scalp electrode (maternal infectious disease, inheritable clotting disorder), and the presence of fetal cardiac arrhythmias, or language barriers. Of the 50 patients in active labour who were included in the original study, 36 women received LEA on patient request; 23 were included in this pilot study, as electrohysterography recording was incomplete in 13 cases (Supplementary Material Figure S1).

In the 30 minutes before LEA initiation, intravenous normal saline 500 mL was administered. Maternal heart rate, blood pressure, and oxygen saturation were monitored, as per institutional practice. The blood pressure measurement obtained immediately before the start of the epidural procedure served as the baseline blood pressure. The most recent cervical dilation measured within the 2 hours of initiating analgesia was recorded. The electrophysiological cardiotocogram (CTG) registration continued without interruption during and after epidural analgesia initiation. With the woman in a sitting position, an epidural catheter was sited between L1 and L5. An epidural test dose of bupivacaine 0.25% 3 mL with 1:200,000 adrenaline was administered, followed within a few minutes by an additional 5-7 mL of the same solution. A continuous infusion of ropivacaine 0.1% with sufentanil 0.5 mcg/mL at 8-10 mL/hour was initiated to maintain analgesia.

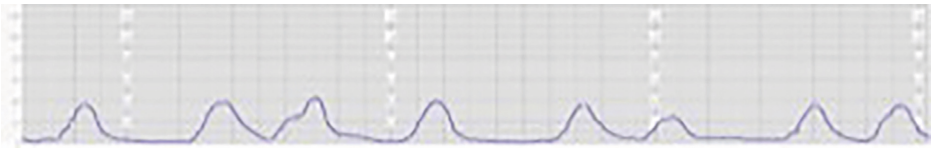
Uterine contraction frequencies were extracted from the electrohysterography-derived tocogram, generated by the Nemo® Fetal Monitoring System (NFMS) (Nemo Healthcare B.V., Veldhoven, The Netherlands). The NFMS consists of a base, a link, and a self-adhesive patch incorporating six electrodes (Fig. 1) that measures electrical activity on the abdominal surface.

Fig. 1. The NFMS (Nemo® Fetal Monitoring System, Nemo Healthcare B.V., Veldhoven, The Netherlands) consists of a base, a link and a self-adhesive patch incorporating six electrodes.

Extraneous electrical activity from sources such as abdominal musculature and the maternal and fetal cardiac myometrium is suppressed by incorporated band-pass filters between 0.3 and 0.8 Hz.[9,11] The remaining bioelectrical activity measured by the NFMS reflects the uterine-generated and propagated action potentials, which underlie uterine muscle contractions.[11] Electrohysterography data are processed in real-time by the NFMS and converted into a measure of uterine activity, which correlates with intrauterine pressures based on a mathematical model.[11] After processing and converting all NFMS data, a real-time CTG waveform is generated for clinical decision-making (Fig. 2).[11,14]

For this study, a locally developed tool for uterine activity annotation was used to analyse the electrohysterography-derived tocograms. One researcher annotated the onset and offset of each uterine contraction and manually eliminated all artefacts from the electrohysterography recordings. Artifacts were visually recognized by specific waveforms.[9] Another investigator was consulted in case of doubt regarding the onset and offset of uterine contractions and this second investigator randomly checked approximately one third of all recordings to confirm accurate contraction detection.[11,13] Both investigators were blinded to fetal heart rate tracings and clinical information during the annotation of the recordings, except for the timing of LEA initiation.

Fig. 2. Example of an electrohysterography recording, as processed real-time by the NFMS.



The mean contraction frequency was defined as the contraction frequency per 10 minutes, derived from 30-minute averages, according to the International Federation of Gynecology and Obstetrics (FIGO) recommendations.[15] The 30-minute windows used for this analysis were nonoverlapping. The mean contraction frequency was extracted from the 60 minutes before and until 120 minutes following LEA initiation, divided into 30-minute phases; phase 0 between 60 and 30 minutes before LEA initiation, phase 1 between 30 minutes before and LEA initiation, phase 2 starting at LEA initiation (test dose) until 30 minutes following LEA initiation, phase 3 between 30 and 60 minutes, phase 4 between 60 and 90 minutes and phase 5 between 90 and 120 minutes following LEA initiation, respectively. All patient-related obstetric and anaesthetic data were obtained from the electronic patient data management system.

All continuous variables were reported as median with interquartile range (25% and 75% quantiles), while counts and percentages were used for binary and categorical variables. The outcome variable (average contraction frequency per 10 minutes) was modelled using a linear mixed model to account for the repeated measurements. For the primary analysis, a dichotomous variable (before vs. after epidural initiation) was included in the model to estimate the difference between the average contraction frequency in the 60 minutes before LEA initiation (phases 0 and 1) and the average contraction frequency in the 120 minutes following LEA initiation (phase 2 to 5).

The linear mixed model included variables that might have a confounding effect on the outcome measure (average contraction frequency per 10 minutes): oxytocin infusion rate at the start of each 30-minute phase, cervical dilation before initiation of epidural analgesia, labour initiation (spontaneous/induced), and maternal hypotension defined as >20% reduction of systolic blood pressure from baseline with epidural analgesia initiation (yes/no). The choice of the (Toeplitz) correlation structure for the residuals was performed based on AICC (Akaike information criterion, corrected for small sample sizes), BIC (Bayesian information criterion), and visual inspection of the residuals. In case of discordant conclusions from the AICC and BIC, the indication from the AICC was followed unless the choice visibly led to a violation of the assumptions on the residuals. To evaluate the longitudinal trend in time in the average contraction frequency, we fitted the same model as for the primary analysis but replaced the dichotomous variable with the phase number as a categorical variable to avoid making an a priori assumption on the shape of the trend. The phase directly preceding epidural analgesia initiation was defined as the reference (phase 1). Statistical analyses were performed using SAS Software 9.4, PROC MIXED. A P value of <0.05 (two-tailed) was considered statistically significant.

Table 1. Baseline characteristics of the study population.

	Value (n = 23)
Age (years)	32.0 [29.0, 34.0]
Body Mass Index (kg/m^2)	24.7 [22.8, 32.5]
Gestational age (weeks + days)	39 + 0 [38 + 0, 40 + 3]
Nulliparous, n	13 (56.5%)
Induction of labour, n	18 (78.3%)
Cervical dilation before labour epidural analgesia initiation (cm)	4.0 [3.0, 5.0]
Oxytocin use during study period, n	18 (78.3%)
Mode of delivery	
Spontaneous vaginal delivery, n	17 (73.9%)
Assisted vaginal delivery, n	1 (4.6%)
Caesarean delivery, n	5 (21.7%)

Data presented as median with interquartile range [IQR] or number of patients (%).

RESULTS

The summary statistics of baseline characteristics of all included cases (N = 23) are presented in Table 1. After LEA initiation, eight cases of maternal hypotension (defined as a >20% reduction of systolic blood pressure) occurred; one patient received an extra bolus of IV fluid as treatment. No patient received a tocolytic agent during the study period. During the 120 minutes following LEA initiation, the average contraction frequency was lower compared to the 60 minutes before LEA initiation (-0.37 contractions/10 minutes [95% CI -0.64 to -0.11]; P = 0.007) (Table 2). The estimated effect of possible confounders (i.e. oxytocin infusion rate at the beginning of each phase, maternal hypotension, labour induction, and cervical dilation) was not statistically significant, but these variables were kept in the model as a correction because they were expected to affect uterine activity from a clinical standpoint. The calculated mean contraction frequencies per 10 minutes in the 30-minute phases are presented in Figure 3.

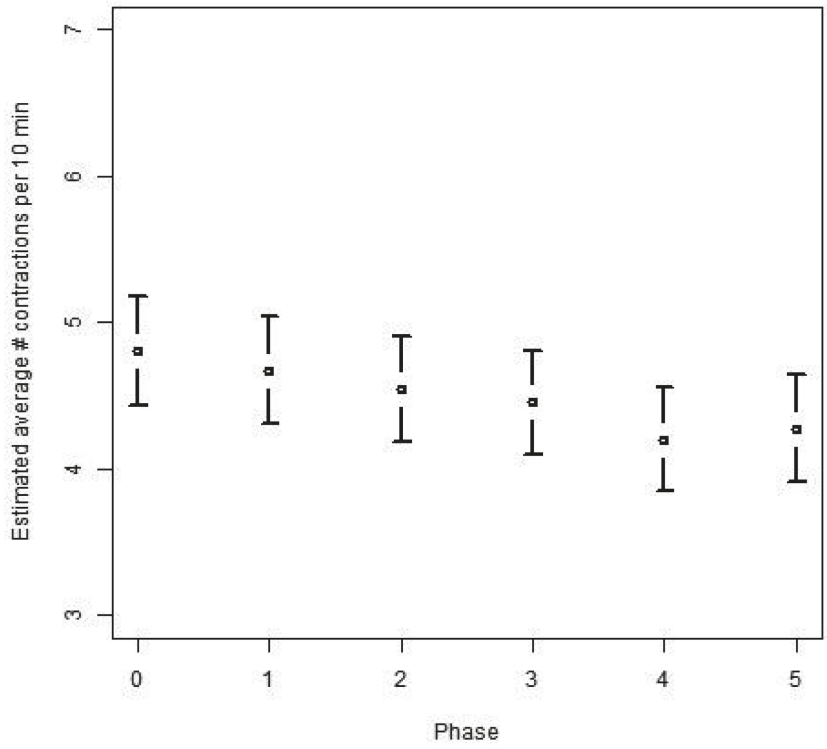
Table 2. Estimates of the fixed effects coefficients.

Effect	Estimate	Standard Error	Pr > |t|	Lower	Upper
Intercept	4.32	0.45	<0.01	3.38	5.25
Start LEA*	-0.37	0.13	0.007	-0.64	-0.11
Oxytocin	27.66	17.86	0.13	-8.06	63.38
SBP drop >20%**	-0.39	0.22	0.09	-0.85	0.07
Induction***	-0.33	0.25	0.21	-0.86	0.2
Dilation	0.16	0.09	0.11	-0.04	0.35

Model with contraction frequency per 10 minutes as outcome, and dichotomous time variable (before/after LEA initiation) as covariate of interest. Oxytocin dosage (U.min^-1^), dilation (cm) and two dichotomous variables: systolic blood pressure drop (>20% decrease from baseline) and start of labour by induction, are included in the model as covariates.
Abbreviations: LEA, labour epidural analgesia; SBP, systolic blood pressure.
** Pre-LEA is reference.*
*** No SBP hypotension is reference.*
**** Spontaneous labour is reference.*

When comparing the uterine contraction frequency in each phase, a statistically significant decreased mean contraction frequency per 10 minutes was found in phase 4 (60-90 minutes following epidural analgesia initiation) compared to the reference phase (phase 1, 30-0 minutes prior to epidural analgesia initiation) (-0.47 contractions/10 minutes [95% CI -0.89 to -0.05]; P = 0.029) (Supplementary Material Table S1).

Fig. 3. Estimated mean contraction frequency per 10 minutes per 30-minute phase.



Phases are plotted on the horizontal axis, phases 0–5 (phase 0: from 60 to 30 minutes before LEA initiation; phase 1: from 30 to 0 minutes before LEA initiation; phase 2: from 0 to 30 minutes after LEA initiation; phase 3: from 30 to 60 minutes after LEA initiation; phase 4: from 60 to 90 minutes after LEA initiation; phase 5: from 90 to 120 minutes after LEA initiation). The estimated mean number of contractions per 10 minutes (95% confidence intervals) are plotted on the vertical axis. The phases before labour epidural analgesia initiation are presented in grey with circle markers, while the phases after initiation are presented in black with triangle markers.

DISCUSSION

This prospective pilot study using electrohysterography to compare the mean uterine contraction frequency before and after LEA initiation identified a reduction in uterine activity in the 2 hours following initiation compared to the hour prior. The decrease was most pronounced 60 to 90 minutes following initiation. However, the average decrease of 0.37 contractions per 10 minutes might be considered clinically negligible as the contraction frequency remained within the normal range per FIGO guidelines.[15] Nevertheless, we found a decreased uterine activity, which may contribute to the persisting association between neuraxial labour analgesia and oxytocin augmentation.[1,16]

To our knowledge, this is the first study using real-time electrohysterography to examine uterine contraction frequency after initiation of LEA in a clinical context. Our study analysed uterine activity up to 2 hours after LEA initiation, a longer evaluation period than in most studies. As each patient acted as their control by comparing contraction frequencies pre- and post-LEA initiation, we did not include comorbidities or parity in our analyses. Variables that might have given insight into LEA effectiveness were also not assessed, such as pain scores or prior analgesics. We used expert-based uterine contraction annotation of the electrohysterography recordings. Intra- and inter-observer disagreements have been demonstrated in electrohysterography derived tocograms.[17] By blinding the researcher to fetal heart rate tracings and clinical information during the annotation, and by assistance of a second researcher for confirmation, we aimed to minimize any discrepancies, although awareness of the time of LEA initiation could have contributed to confounding.[17]

Causality between neuraxial labour analgesia and uterine activity changes has never been convincingly determined and performing well-designed trials to evaluate various analgesic modalities and drugs in labouring patients is challenging.[18] Recording uterine activity alterations provides an additional challenge which results in the use of surrogate outcomes, such as labour duration, mode of delivery, use of oxytocin augmentation, or the occurrence of fetal heart rate abnormalities. Only a handful of recent studies examined the effect of neuraxial labour analgesia techniques on uterine contraction parameters, with conflicting results; increased, decreased and unchanged uterine activity have each been reported.[19-20,2-4]

There are two retrospective studies reporting increased uterine activity following neuraxial labour analgesia, which contradict our findings.[3,19] Heuser et al. identified LEA as a risk factor for tachysystole (defined as >5 contractions in 10 minutes), with a relative risk of 1.55 (95% CI 1.37 to 1.74).[3,21] The second study, in patients at risk for uteroplacental insufficiency, observed a statistically significant increase in fetal heart rate abnormalities after either LEA or combined spinal-epidural analgesia (CSE) initiation.[19] Fetal heart rate abnormalities served as a surrogate for either increased uterine activity and/or maternal hypotension, although there was no increase in the rate of systolic blood pressure <100 mmHg. LEA and CSE analgesia were both associated with statistically significant increased rates of uterine hypertonus, defined as a uterine contraction lasting longer than 2 minutes, while LEA initiation was also associated with increased rates of tachysystole.[19]

Our findings align with three studies reporting decreased or unchanged uterine activity following epidural analgesia initiation.[2,4,20] One prospective study compared the effects of LEA and CSE analgesia on the first stage of labour, using external tocodynamometry to monitor uterine activity, assessed as augmented, reduced, or unchanged, without further specification.[4] There was no difference in first-stage labour duration; however, a statistically significant uterine activity reduction was reported in women following initiation of LEA compared with CSE analgesia.[4] One retrospective study using an IUPC found no significant

changes in contraction frequency during the first 60 minutes following LEA initiation, which does not contradict our findings since the statistically significant reduction of uterine contraction frequency found in our study occurred 60 to 90 minutes following LEA initiation. [2] One case-control study used electrohysterography and external tocodynamometry simultaneously to compare uterine activity in women with and without patient-controlled epidural analgesia (PCEA).[20] They only analysed bursts of electrical activity occurring during contractions, which were verified by external tocodynamometry. All electrohysterography parameters, as well as the tocodynamometry-determined contraction frequency, were significantly lower after the initiation of PCEA compared with the control group. The largest reductions occurred 30 minutes after PCEA initiation, earlier than in our study, as we found the largest decrease in uterine contraction frequency to occur 60 to 90 minutes after LEA initiation. We believe these conflicting results not only show the wide variety of neuraxial labour analgesia approaches, the range of clinical circumstances, and the different measurement techniques and study designs, but they also demonstrate the lack of proper understanding of the underlying (patho)physiology.

There are several possible explanations for the direct or indirect effect of neuraxial labour analgesia on uterine activity. Local anaesthetics and opioids display direct depressant effects on the myometrium in vitro, however only in much higher concentrations than detected in plasma during neuraxial labour analgesia in vivo.[22-23] Intravenous fluid boluses, local anaesthetics with adrenaline and opioids may change uterine action potentials or intracellular calcium concentrations and thus indirectly affect uterine activity.[24-25] Rapid administration of an intravenous fluid administration (e.g. 1 L) may temporarily reduce uterine contractility, possibly through decreasing vasopressin and oxytocin release from the posterior pituitary gland.[26-30] However, the late uterine activity changes found in our study suggest that the pre-procedure fluid bolus was unlikely the cause of the decreased uterine activity. Epidural adrenaline may elicit a systemic beta-adrenergic tocolytic effect, which has been associated with a prolonged first stage of labour and increased oxytocin augmentation.[31-32] In our study, epidural adrenaline was only used once with the initial epidural dose, while we observed the largest reduction of uterine activity 60 to 90 minutes following LEA initiation. Thus, epidural adrenaline is an unlikely cause for the observed effect, especially given other studies that describe changes in uterine activity without epidural adrenaline administration. [4,20] Epidural opioids can reduce plasma concentrations of endogenous oxytocin during labour.[33-34] There was no opioid given with LEA initiation, but sufentanil was administered for LEA maintenance in the epidural infusion. This could explain the reduced contraction frequency we observed later compared with other studies. The late decrease in uterine activity could also be attributable to the different local anaesthetics used for initiation (bupivacaine) and maintenance (ropivacaine) of analgesia, as different inhibitory effects on uterine activity may exist.[35]

The use of electrohysterography in clinical practice may provide, apart from more reliable CTG monitoring, a tool to study labour physiology and the impact of clinical interventions

such as LEA.[2,36] By using electrohysterography, other parameters can also be examined in addition to the uterine contraction frequency such as entropy or conduction velocity. These parameters may offer more insight into the causal mechanism of the effects found in this study.

This small observational pilot study was conducted in a single hospital, with each patient serving as their control (i.e. before versus after initiation of LEA). While LEA procedures were consistent, the inability to blind participants and researchers to the time of intervention might introduce bias. Unknown confounding factors could be present, and the limited observation period may exclude long-term effects. More studies are needed to validate our observation.

In conclusion, using electrohysterography to assess uterine contractility, we observed a statistically significant reduction of 0.37 contractions per 10 minutes after LEA initiation, with the largest reduction occurring 60 to 90 minutes after initiation of LEA. It is not clear whether this decrease is clinically significant, but it demonstrates that electrohysterography can be used to identify changes in uterine contractility. Further examination of the underlying relevant electrophysiology and exploration of electrohysterography applications in clinical anaesthesia and obstetric research are needed to improve peripartum safety and increase our knowledge of how uterine contractility is affected by common interventions and medications during labour.

SUPPLEMENTARY DATA

Fig. S1. STROBE diagram of patient recruitment and data analysis

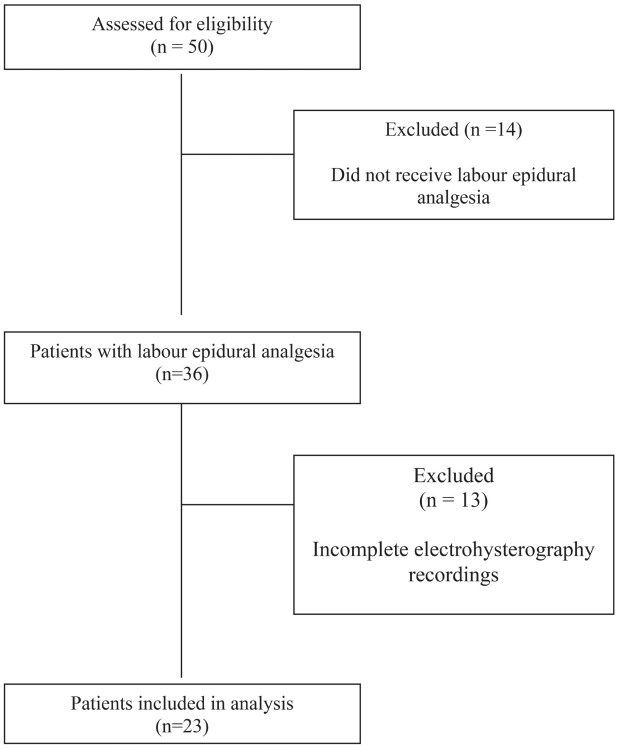


Table S1. Estimates of the fixed effects coefficients.

Effect		Estimate	Standard Error	Pr >|t|	Lower	Upper
Intercept		4.28	0.5	<.01	3.34	5.22
Phase*	0	0.13	0.20	0.51	-0.27	0.53
	2	-0.13	0.22	0.56	-0.56	0.3
	3	-0.22	0.18	0.21	-0.57	0.13
	4	-0.47	0.21	0.03	-0.89	-0.05
	5	-0.40	0.21	0.06	-0.81	-0.01
Oxytocin		25.1	17.74	0.16	-10.48	60.5
SBP drop >20%**		-0.38	0.22	0.10	-0.84	0.08
Induction***		-0.33	0.25	0.20	-0.86	0.19
Dilation		0.15	0.09	0.11	-0.04	0.35

Model with contraction frequency per 10 minutes as outcome and phase as categorical time variable as covariate of interest. Oxytocin dosage (U.min^{-1}), dilation (cm) and two dichotomous variables: systolic blood pressure drop (>20% decrease from baseline) and start of labour by induction, are included in the model as covariates.

Phase 0 from 60 to 30 minutes before LEA initiation, phase 1 from 30 to 0 minutes before LEA initiation, phase 2 from 0 to 30 minutes after LEA initiation, phase 3 from 30 to 60 minutes after LEA initiation, phase 4 from 60 to 90 minutes after LEA initiation, phase 5 from 90 to 120 minutes after LEA initiation.

Abbreviations: LEA, labour epidural analgesia; SBP, systolic blood pressure.

**Phase 1, from 30 minutes to 0 minutes before LEA initiation is the reference.*

***No SBP hypotension is the reference.*

****Spontaneous labour is the reference.*

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Chapter 3

Intrathecal morphine does not prevent chronic postsurgical pain after elective Caesarean delivery: a randomised controlled trial

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ABSTRACT

Background

Morphine is frequently added to spinal anaesthesia for Caesarean delivery. We aimed to determine whether intrathecal morphine for spinal anaesthesia decreases the risk of chronic postsurgical pain (CPSP).

Methods

In this randomised, double-blind, placebo-controlled trial, 290 healthy parturients undergoing elective Caesarean delivery were randomly assigned in a 1:1 ratio to receive either intrathecal morphine 100 mcg (n=145) or normal saline (control; n=145) as a part of spinal anaesthesia. Anaesthetic care and postoperative pain management were standardised in all patients. The primary outcome was the incidence of CPSP at 3 months. Secondary outcomes included CPSP at 6 months, pain severity, and pain interference, measured by the Brief Pain Inventory questionnaire using an 11-point numeric rating scale, at 3 and 6 months after the surgery.

Results

Two hundred and seventy-six patients completed the 3-month follow-up, 139 in the morphine group and 137 in the placebo group. The incidences of CPSP at 3 months were 19% (27 of 139) in the morphine group and 18% (25 of 137) in the placebo group (odds ratio, 1.08; 95% confidence interval, 0.59-1.97; P=0.803). At 6 months, CPSP was present in 23 of 139 (16%) morphine group patients compared with 19 of 137 (14%) in the placebo group (odds ratio, 1.23; 95% confidence interval, 0.63-2.38; P=0.536). Brief Pain Inventory questionnaire scores for pain severity and pain interference at 3 and 6 months were similar between groups.

Conclusions

Administration of morphine 100 mcg as a component of spinal anaesthesia for elective Caesarean delivery failed to reduce the incidence of chronic pain at 3 and 6 months after surgery.

INTRODUCTION

The incidence of chronic postsurgical pain (CPSP) after Caesarean delivery is reported to be in the range between 7 and 30%, reflecting it to be a significant clinical problem.[1] Studies related to prevention of progression of acute post-Caesarean delivery pain to its chronicity are sparse. Severe acute postoperative pain has been consistently linked with chronic post-Caesarean delivery pain.[1] Therefore, effective analgesia in the perioperative period may mitigate the development of persistent pain.

Current guidelines on analgesia recommend the inclusion of long-acting intrathecal (i.t.) opioids to spinal anaesthesia for acute post-Caesarean delivery pain relief.[2] Despite its frequent use, randomised clinical trials related to intrathecal morphine use and its association with chronic pain are lacking. A recent prospective observational study revealed a significant reduction in chronic pain after Caesarean delivery when morphine was used as an adjuvant to spinal anaesthesia.[3] The primary objective of our trial was to compare the effect of morphine with placebo, added to spinal anaesthesia, on the development of chronic pain, 3 months after elective Caesarean delivery. Our secondary objective was to determine the incidence of chronic pain after 6 months, and to assess pain severity and interference scores using the short form Brief Pain Inventory (BPI) at 3 months and 6 months after Caesarean delivery between the morphine and placebo group. We hypothesised that spinal morphine would reduce the incidence of persistent pain after Caesarean delivery.

METHODS

This prospective, randomised, double-blind trial was conducted at BP Koirala Institute of Health Sciences (BPKIHS) between April 2018 and March 2021. The study protocol was approved by the institutional review committee (BPKIHS; IRC number: IRC/1183/017). The trial was registered before patient enrolment at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03451695; Principal Investigator: AS; date of registration: March 2, 2018). All participants provided written informed consent, and the trial was conducted in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines.

We enrolled full-term singleton parturients with American Society of Anesthesiologists (ASA) physical status 2 undergoing planned Caesarean delivery under spinal anaesthesia. Exclusion criteria were age <18 yr, contraindication to spinal anaesthesia, preeclampsia, height <150 cm, ASA physical status >2, BMI >40 kg m^{-2}, allergy to any drug used in the study, recent opioid exposure, substance abuse, significant cardiovascular, renal, or hepatic disease, and known fetal abnormalities. Consent for the participation in the study was obtained during pre-anaesthetic visits in the evening before surgery. During this visit, patient baseline characteristics (maternal age, height, weight, BMI, gestational age, socioeconomic background, previous Caesarean delivery, pre-existing chronic pain) were documented. The

Kuppuswamy scale adapted for Nepali population was used for assessing socioeconomic status and the scoring was based on education, occupation, and total monthly family income (26-29: upper class, 16-25: upper middle class, 11-15: lower middle, 5-10: upper lower, <5: lower class).[4] Also, preoperative anxiety level (assessed with hospital anxiety and depression scale),[5] pain catastrophising (assessed with pain catastrophising scale),[6,7] and preoperative pain sensitivity (assessed with pain pressure threshold and tolerance using a handheld pressure algometer; details provided in the Supplementary Data S1.)[8] were recorded. The investigator also educated the patients regarding the use of numeric rating scale (NRS) scores for postoperative pain and satisfaction.

Eligible consented patients were randomly assigned in a 1:1 ratio to one of the two groups (morphine and placebo groups). We randomised participants using the sequentially numbered, opaque sealed envelopes (SNOSE) technique. A randomisation list was generated in a variable block size of 4/6/8 using the online software (www.sealedenvelope.org) by the anaesthesia clerk. To ensure allocation concealment, the same anaesthesia clerk (SA) prepared the randomly generated number for each patient in an opaque envelope, numbered each envelope sequentially, and sealed it. On the day of surgery, SA handed the envelope to an anaesthesia assistant not involved in the trial. The participants, care providers, and investigators were unaware of the trial-group assignments.

On arrival to the operating room, standard monitoring (noninvasive BP, ECG, and pulse oximetry) was applied. Before administration of spinal anaesthesia, the anaesthesia assistant opened the envelope and prepared the study drug solution accordingly. The anaesthesiologist blinded to the group assignment administered spinal anaesthesia in the lateral position at the L3-L4 or L4-L5 interspace using a spinal needle. The morphine group received i.t. hyperbaric bupivacaine 11 mg (2.2 ml 0.5%), fentanyl 10 mcg (0.2 ml), and preservative-free morphine 100 mcg (0.1 ml). The placebo group received hyperbaric bupivacaine 11 mg (2.2 ml 0.5%), fentanyl 10 mcg (0.2 ml), and normal saline (0.1 ml). A co-loading with i.v. Ringer's lactate solution, 10 ml kg^{-1} was initiated immediately after spinal injection. Patients were positioned supine with a left lateral tilt. Surgery was started once the sensory level tested with pinprick reached T6 or higher. All patients received i.v. ondansetron 4 mg. Hypotension was managed with either phenylephrine or ephedrine at the discretion of the anaesthesiologist. Standard surgical procedures for Caesarean delivery were followed that included Pfannenstiel incision and leaving the peritoneum unsutured at the time of closure. The paediatrician recorded the Apgar score at 1 and 5 min after delivery of the baby.

At the end of surgery, the obstetrician injected bupivacaine 0.25% s.c. in the surgical wound (15 ml in each of the upper and lower sides). Also, ketorolac 30 mg i.v., every 8 h and paracetamol 1 g i.v., every 6 h were administered. After 24 h, they received oral aceclofenac 100 mg every 12 h, and paracetamol 1 g every 6 h. Pain during the first 48 h was treated with i.v. morphine 2 mg every 5 min, keeping the NRS score ≤3. In the PACU, patients were observed for approximately 2 h and subsequently transferred to the postnatal unit. Postoperative pain

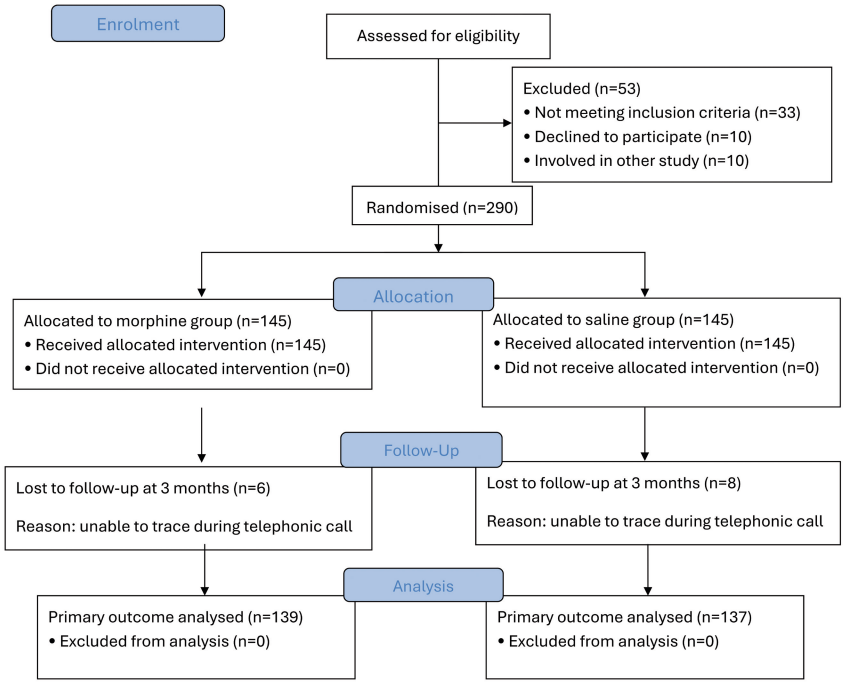
severity was assessed using an 11-point NRS (0=no pain and 10=the worst possible pain) at 2, 6, 12, 24, and 48 h after CS. Patients were asked to rate their pain scores both at rest and movement. The area of hyperalgesia around the surgical incision was assessed at 48 h postoperatively using a 256-mN von Frey filament (Bioseb; In Vivo Research Instruments, Vitrolles, France). The test was started along four points horizontally and perpendicularly around the surgical wound. It was initiated at a 5 cm point away from the wound and moving in the direction of wound at 5 mm intervals until the patient reported a painful, sore, or sharp feeling. If there was no change in sensation, the test was stopped at 5 mm to the incision. The measurements were registered to calculate the total area of hyperalgesia (in cm^2) as described previously.[9,10] At 48 h, patient satisfaction from postoperative analgesia was assessed using a 5-point scale (1=highly satisfied, 2=satisfied, 3=neutral, 4=not satisfied, and 5=strongly dissatisfied). After discharge from hospital (at 48 h), oral aceclofenac (100 mg) twice daily and paracetamol 1 g, four times per day were prescribed for 3 days. For breakthrough pain during this period patients were asked to take tramadol 50 mg orally as required. At 8 weeks postpartum, patients were assessed for depression using the Edinburgh postnatal depression scale (EPDS).[11]

For assessment of CPSP, patients were contacted by telephone by one of the blinded investigators (YT) at 3 and 6 months after the surgery. CPSP was defined as pain that developed after Caesarean delivery and lasted for at least 3 months after surgery, with the pain being different from other pre-existing pain conditions before surgery.[12] The patients who reported CPSP were asked to answer the short form BPI questionnaire, which contains four questions on pain severity and seven questions on pain interference.[13,14] Pain was rated on a verbal NRS (0-10), with 0='no pain' or 'no interference' and 10='worst possible pain' or 'complete interference'. Participants rated their worst, least, and average pain during the past 24 h and their pain at the time of interview. Participants were also asked to rate the level that pain interferes with daily activities on seven aspects of life (general activity, mood, walking, work, relationship with others, sleep, and enjoyment of life). The primary outcome was the frequency of CPSP at 3 months after surgery. Secondary outcomes were CPSP at 6 months, and BPI scores at 3 and 6 months after surgery.

Sample size and statistical methods

A previous prospective observational study reported the incidence of persistent pain at 3 months after Caesarean delivery to be 46% in those who did not receive i.t. morphine and 28% in those who received i.t. morphine.[3] To detect this difference, with 80% power, at a two-sided significance level of 0.05, we estimated a sample of 123 subjects in each group (Stata version 15, StataCorp, College Station, TX, USA). To account for 15% loss to follow-up, we recruited and randomised a total of 290 patients.

Fig. 1. Consolidated Standards of Reporting Trials flow diagram of the study.



Normality of the data was assessed using a histogram visually and verified using the Shapiro-Wilk test. The Student's unpaired t-test was used for comparing normally distributed data between groups, and the Mann-Whitney rank sum test for non-normally distributed data. Proportions between groups were analysed using the χ^2 test or Fisher exact test, as appropriate. Treatment effects on the incidences of CPSP were presented as odds ratio, with a 95% confidence interval (CI). For NRS pain scores over a period of 48 h, we calculated the area under the curve (AUC) using the trapezoidal rule. Next, time-weighted average pain during the first 48 h for each patient was obtained dividing the AUC by the time interval between the first (2 h) and the last (48 h) NRS measurements. Statistical analysis was performed using Stata version 15. A 2-sided P-value <0.05 was considered as statistically significant.

RESULTS

Of 290 patients randomised, 145 received i.t. morphine and 145 did not receive i.t. morphine; 14 patients were lost to follow-up (Fig.1). The complete case analysis for primary outcome involved 276 patients (139 in the morphine group and 137 in the control group). We carried out a complete case analysis because we assumed that the data for the primary outcome were missing completely at random (unable to trace during telephone call). Patient characteristics,

preoperative anxiety level and pain catastrophising scores, pain pressure threshold, and pain pressure tolerance are shown in Table 1.

Table 1. Baseline patient characteristics and preoperative data.

Variables	Morphine group n=139	Saline group n=137	*P*-value
Age (yr)	28.29 (4.88)	28.16 (4.74)	0.816
BMI (kg/m^2)	27.41 (3.66)	27.46 (3.69)	0.915
Gestational age (weeks)	38.81 (1.26)	38.71 (1.16)	0.505
Ethnicity			0.826
Tibeto-Mongolian	54 (39)	55 (40)	
Indo-Aryan	85 (61)	82 (60)	
Previous Caesarean delivery	94 (68)	91 (66)	0.832
Pre-existing chronic pain	4 (2)	2 (1)	0.684
Socioeconomic status			0.498
Upper class	6 (4)	12 (9)	
Upper middle class	68 (49)	63 (46)	
Lower middle class	41 (30)	41 (30)	
Upper lower class	24 (17)	21 (15)	
HADS (0-21)			
Anxiety	4 (3-6)	4 (3-6)	0.394
Depression	3 (2-4)	3 (2-5)	0.406
Pain catastrophising scores (0-52)	8 (5-13)	8 (6-12)	0.976
Pain pressure threshold (kg)	4.37 (1.26)	4.32 (1.28)	0.766
Pain pressure tolerance (kg)	6.74 (1.53)	6.62 (1.36)	0.517

Values are expressed as mean (standard deviation), number (%), or median (inter-quartile range).
Abbreviation: HADS, Hospital Anxiety and Depression Scale.

Table 2. Postoperative data.

Variables	Morphine group n=139	Saline group n=137	*P*-value
Duration of surgery (min)	60 (45-60)	55 (45-60)	0.123
Pain at rest, up to 48 h*	2.26 (0.72)	2.60 (0.82)	<0.001
Pain during movement, up to 48 h*	3.24 (0.77)	3.63 (0.81)	<0.001
I.V. morphine used up to 48 h (mg)	6 (4-8)	8 (6-10)	<0.001
Severe pain up to 24 h (NRS ≥7)	6 (4)	14 (10)	0.059
Severe pain up to 48 h (NRS ≥7)	10 (7)	19 (14)	0.071
Secondary hyperalgesia at 48 h (cm2)	51 (17-76)	39 (19-80)	0.819
Satisfaction, postoperative analgesia			0.400
Highly satisfied	20 (14)	16 (12)	
Satisfied	85 (61)	73 (53)	
Neutral	27 (19)	36 (26)	
Dissatisfied	5 (4)	9 (7)	
Strongly dissatisfied	2 (1)	3 (2)	
EPDS scores ≥11 (8 weeks)	10 (7)	14 (10)	0.373

*Values are expressed as median (inter-quartile range), mean (standard deviation), number (%). Abbreviations: EPDS, Edinburgh postnatal depression scale; NRS, numeric rating pain scale scores. *Summary statistics of pain scores are reported as mean (standard deviation) of time-weighted average pain during the first 48 h.*

Immediate postoperative outcomes and outcomes after hospital discharge (EPDS scores) are shown in Table 2. The pain scores (on rest and during movement) at different time points up to 48 h are shown in Supplementary Table S1. The time-weighted average postoperative pain scores and total morphine requirements up to 48 h were significantly higher in the saline group than the morphine group (Table 2). However, no difference was detected in terms of acute severe postoperative pain.

Overall, 52 (18%) patients reported CPSP at 3 months. CPSP at 3 months was diagnosed in 27 (19%) patients assigned to receive i.t. morphine, compared with 25 (18%) patients in the saline group (odds ratio in the morphine group, 1.08; 95% CI, 0.59-1.97; P=0.803) (Fig. 2). The incidence of CPSP at 6 months did not differ significantly between the two groups: morphine 23 of 139 (17%) vs saline 19 of 137 (14%), odds ratio in the morphine group 1.23 (95% CI, 0.63-2.38; P=0.536). We detected no significant differences between the two groups for the BPI pain severity and pain interference scores at 3 and 6 months after surgery (Table 3).

Fig 2. Incidence of chronic postsurgical pain at 3 and 6 months after surgery.

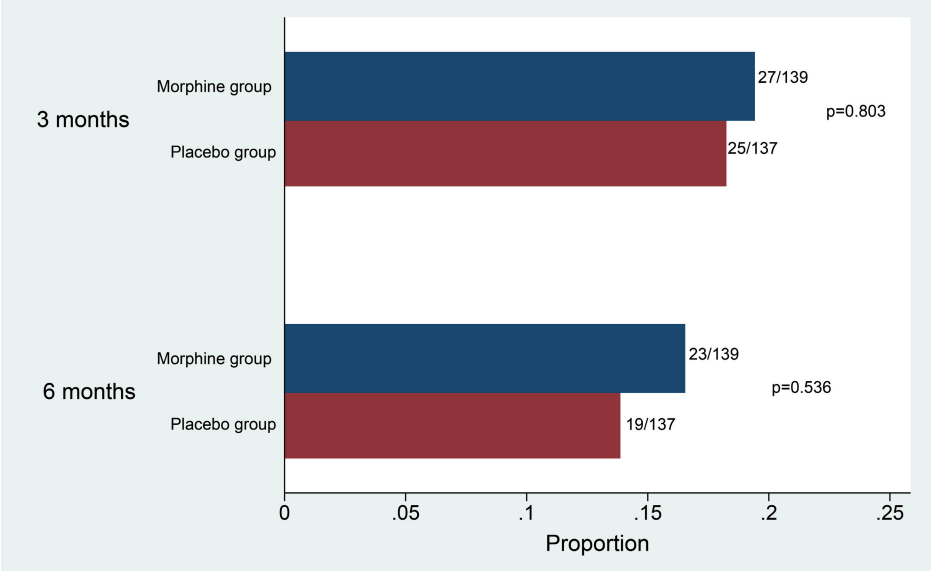


Table 3. Description of chronic postsurgical pain at 3 and 6 months after surgery.

	3 Months			6 Months		
	Morphine group n=27	Saline group n=25	*P*-value	Morphine group n=23	Saline group n=19	*P*-value
BPI pain severity*						
Worst pain in past 24 h	3.51 (1.15)	3.76 (0.83)	0.296	2 (0.67)	2.36 (0.76)	0.116
Least pain in past 24 h	1.85 (0.71)	2.04 (0.61)	0.297	1.60 (0.72)	1.57 (0.90)	0.882
Average pain in past 24 h	2.22 (0.84)	2.52 (0.87)	0.222	1.91 (0.59)	2.21 (0.71)	0.14
Current pain	2.18 (0.87)	2.36 (0.70)	0.28	1.60 (0.89)	1.68 (0.88)	0.76
BPI pain interference*						
General activities	2.14 (0.86)	2.56 (0.96)	0.186	1.56 (0.84)	1.78 (0.63)	0.457
Mood	1.33 (1.03)	1.92 (1.55)	0.196	1.65 (0.64)	1.89 (0.73)	0.209
Walking ability	1.18 (1.07)	1.84 (1.57)	0.128	1.34 (0.77)	1.57 (1.07)	0.727
Normal work	1.25 (1.05)	1.96 (1.56)	0.101	1.21 (0.90)	1.47 (1.12)	0.436
Relations with other people	0.96 (0.93)	1.60 (1.38)	0.086	1.43 (0.66)	1.78 (0.91)	0.133
Sleep	1.33 (1.17)	1.76 (1.58)	0.393	1.47 (0.59)	1.68 (1.00)	0.338
Enjoyment of life	1.03 (0.97)	1.56 (1.32)	0.151	1.39 (0.65)	1.47 (1.02)	0.745

Values are expressed as mean (standard deviation).
Abbreviations: BPI, brief pain inventory.
**BPI pain severity and pain interference assessed by numeric rating scale scores (0-10) and analysed by Mann-Whitney U-test.*

DISCUSSION

In this clinical trial, we were unable to demonstrate a significant difference in the incidence of chronic pain after planned Caesarean delivery at 3 and 6 months between the parturients who received i.t. morphine and the parturients who did not receive i.t. morphine for spinal anaesthesia. Furthermore, between the morphine and the placebo groups, there was no significant difference in the BPI scores for pain severity and pain interference during the 3- and 6-month follow-up in patients who reported CPSP.

Caesarean delivery is one of the commonly performed surgeries worldwide, and >10% of parturients report persistent pain afterwards.[1,15] CPSP after surgery is a significant clinical problem, as it adversely impacts the parturients quality of life and may compromise infant care. Reports have shown a consistent association between severe acute postoperative pain and CPSP after Caesarean delivery.[1] Therefore, application of a multimodal analgesic regimen that includes long-acting neuraxial opioids is beneficial. Moriyama and colleagues[3] reported in their observational study that i.t. morphine 100 mcg decreased the incidence of a CPSP after Caesarean delivery (adjusted odds ratio 0.424; 95% CI 0.202-0.889, P=0.023). Surprisingly, in the study by Moriyama and colleagues,[3] there was no significant difference in the acute postoperative pain and the reasons as to how i.t. morphine decreased the incidence of CPSP was also not mentioned.

Intrathecal morphine acts in various levels of pain pathways (spinal and supraspinal) and provides prolonged duration of analgesia (up to 24 h).[16] Because i.t. morphine is effective in reducing the intensity of early postoperative pain, we hypothesised that it may indirectly decrease the incidence of CPSP. This assumption is also supported by a meta-analysis which showed a reduction in CPSP with the use of neuraxial anaesthesia.[17] However, our clinical trial failed to demonstrate the protective role of i.t. morphine. One reason could be because we had used i.t. fentanyl and multimodal analgesia (including local anaesthetic infiltration at the incision site) in both groups and, therefore, it did offer some protection in the placebo group. The other reason is that single shot i.t. morphine may not have any beneficial role in the late postoperative period. Because the transition from acute to CPSP is complex in nature, continuation of preventive modalities beyond the early postoperative period may be beneficial in high-risk groups. However, such modalities in the obstetric population are practically challenging because of safety, ethical, and feasibility issues.

The mechanism of CPSP is partly explained by central sensitisation, a phenomenon of neuronal hyperactivity and hyperexcitability in the spinal cord and brain that occurs after surgical insult.[18] Animal studies have shown that i.t. morphine has inhibitory effects on nociception in the spinal dorsal horn.[16,19,20] However, whether this analgesic mechanism of i.t. morphine is sufficient to attenuate central sensitisation is not fully elucidated. In fact, intrathecally administered morphine has shown conflicting results in a chronic pain model.[21] For example, in a model of sustained nociception, it produced analgesic effects,[22,23]

whereas others reported that it is less effective in animal models of chronic neuropathic pain.[24,25] Notably, contradictory findings in the previous studies may be attributable to differences in the timing of its administration.

Secondary mechanical hyperalgesia (i.e. increase pain sensitivity outside the area of the wound) is the consequence of central sensitisation,[26] and it may be a prognostic marker for the subsequent development of persistent pain.[27-29] The modulatory effects of i.t. morphine on nociception-induced hyperalgesia in animal models of postoperative pain remains unclear.[30,31] Intrathecal morphine (both pre-incisional and post-incisional), in comparison with the saline, did not result in a significant reduction in mechanical hyperalgesia beyond 5 h of incisional pain in a rat model.[30] In healthy volunteers, administration of systemic morphine in experimentally induced secondary hyperalgesia showed inconsistent results,[32-34] whereas clinical studies on i.t. morphine and secondary hyperalgesia are lacking.

Although it was statistically insignificant, we observed an increased area of secondary hyperalgesia in the i.t. morphine group as compared with those who did not receive i.t. morphine. Whether this paradoxical finding is attributed to opioid-induced hyperalgesia (OIH) is a matter of debate. In laboratory and clinical studies, chronic administration of spinal morphine is linked to the genesis of OIH, suggesting that OIH is dose- and time-dependent.[35] Interestingly, even acute exposure to opioid can produce OIH. A single dose of spinal fentanyl for Caesarean delivery increased postoperative i.v. morphine requirements.[36] However, because of the limited data, it is inconclusive that a single dose of spinal morphine contributes to the development of OIH. Moreover, as a result of the poorly understood mechanism of OIH and lack of standardised pain sensitivity tools to diagnose OIH, it is difficult to establish a causal relationship between perioperative i.t. opioid exposure and the development of OIH. Nevertheless, this is an important area to explore in future studies because of the linkage between postoperative OIH and CPSP.[37]

In our study, we assessed pain interference on quality of life using the BPI questionnaire in patients who reported CPSP at 3 and 6 months after Caesarean delivery. There was no significant difference in BPI scores between patients who received i.t. morphine and patients who did not receive i.t. morphine. Similar to our findings, Foadi and colleagues[38] demonstrated that intrathecally administered morphine was not associated with improved quality of life or physical function at 6 months after knee or hip surgery. This reflects that a single dose of i.t. morphine may not produce long-term beneficial effects despite better perioperative pain control.

There are certain limitations to our study. First, the concept of ‘one size does not fit all’ is growing and the experts have proposed that the effective preventive strategies should be tested in the high-risk group. Unfortunately, a risk prediction tool or scoring system for CPSP after Caesarean delivery is lacking. Development of such validated tools or scoring systems in the future will help to stratify the vulnerable group preoperatively. Second, this trial was

carried out in a single centre situated in Nepal. Third, most reviews/studies on psychosocial risk factors for CPSP have focussed on high-income countries.[39] There may be differences in the psychological and socio-environmental factors between the Nepali and Western population, and therefore, the findings of this study may limit generalisability. Fourth, we used telephonic interview to assess CPSP and BPI questionnaire because we felt that many patients might not visit the hospital after discharge because of financial and logistic reasons. Finally, the follow-up period after surgery was limited to 6 months only.

In conclusion, our study failed to demonstrate any significant advantage of i.t. morphine 100 mcg over placebo on the incidence of CPSP at 3 and 6 months after elective Caesarean delivery. Also, we found no evidence that the use of i.t. morphine affected the pain severity and pain interference at 3 and 6 months after surgery.

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International research grant from the Obstetric Anaesthetists' Association (OAA), United Kingdom.

SUPPLEMENTARY DATA

S1. Assessment of mechanical pain sensitivity before surgery**.**

Mechanical pain sensitivity was assessed using a handheld pressure algometer (FDX®, Wagner Instruments, Greenwich, USA), with a 1-cm^2 rubber tip, and the force value was recorded in kilograms. The device was held perpendicularly on the soft tissue of middle phalanx of the third finger, and the pressure was applied steadily at a constant rate of 1 kg cm^{-2} sec^{-1}. Each participant was instructed about the pressure pain threshold (PPT) and pressure pain tolerance prior to the procedure. Pressure pain threshold (PPT) was defined as the amount of force that elicited pain. The procedure was stopped when the PPT was achieved. Pain tolerance (PT) was defined as the maximum pain that could be tolerated by the participant.

Table S1. Postoperative pain scores.

	Morphine group n=139	Saline group n=137	*P*-value
Pain At Rest, NRS (0-10)			
2 hr	1 (0-2)	1 (0-2)	0.08
6 hr	2 (1-3)	2 (1-3)	0.04
12 hr	2 (1-3)	3 (2-4)	<0.001
24 hr	2 (2-3)	3 (2-3)	0.05
48 hr	2 (2-3)	2 (2-3)	0.32
Pain during movement, NRS (0-10)			
2 hr	1 (0-3)	2 (1-3)	0.13
6 hr	3 (2-4)	3 (2-4)	0.01
12 hr	3 (2-4)	3 (3-5)	<0.001
24 hr	4 (3-4)	4 (3-5)	0.04
48 hr	3 (3-4)	3 (2-4)	0.14

Values are expressed as median (interquartile range)
Abbreviation: NRS, Numeric Rating Scale

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Chapter 4

Association between postpartum depression and chronic postsurgical pain after Cesarean delivery: a secondary analysis of a randomized trial

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ABSTRACT

Purpose

Psychological factors such as anxiety, depression, and catastrophizing, may increase the risk of chronic postsurgical pain (CPSP) following Cesarean delivery (CD). We sought to evaluate whether postpartum depression (PPD) after CD is associated with CPSP and to assess the potential mediating effect of PPD on the relationship between acute severe postoperative pain and CPSP.

Methods

We conducted a secondary analysis of a previous randomized trial. In the original trial, 290 patients undergoing CD in Nepal were randomized to receive either 100 μg of intrathecal morphine or normal saline in addition to their spinal anesthesia with the goal to investigate the relationship between intrathecal morphine use and CPSP development. Eight weeks after CD, we used the Edinburgh Postnatal Depression Scale to identify patients with a provisional diagnosis of PPD (scores ≥12). The study outcomes were the occurrence of CPSP at three and six months.

Results

Out of 276 patients analyzed, 20 (7%) experienced PPD. The incidences of CPSP at three and six months were 18% (52/276) and 15% (42/276), respectively. A multivariable model revealed that the odds of experiencing CPSP at three months postpartum were significantly higher in patients with depression (odds ratio [OR], 4.24; 95% confidence interval [CI], 1.53 to 11.74; P = 0.005) than in those without depression. Similarly, PPD was independently associated with an increased incidence of CPSP incidence at six months post CD (OR, 4.05; 95% CI, 1.42 to 11.54; P = 0.009). Causal mediation analysis showed no mediating effect of PPD between acute severe postoperative pain and CPSP.

Conclusion

In this secondary analysis of a previous randomized trial, we found a significant association between PPD and CPSP following CD.

INTRODUCTION

Chronic postsurgical pain (CPSP), defined as pain persisting for at least three months after surgery, poses significant health challenges after Cesarean delivery (CD).[1] A meta-analysis of 15 studies showed that the incidence of CPSP at three and six months post CD was 15.4% (95% confidence interval [CI], 9.9 to 20.9%) and 11.5% (95% CI, 8.1 to 15.0%), respectively,[2] with one-third of these patients reporting moderate to severe pain. Most studies to date on CPSP after CD have focused on preoperative or immediate postpartum predictors such as preoperative demographics, perioperative psychological issues, surgical techniques, mode of anesthesia, and acute postoperative pain severity.[3,4] Few studies, however, have examined factors in the longer recovery period, such as pain trajectories and mood, and their relationship to CPSP development.

According to the International Classification of Diseases 11th Revision, postpartum depression (PPD) is defined as a major depressive disorder occurring within six weeks after childbirth.[5] The Edinburgh Postnatal Depression Scale (EPDS) is a widely accepted screening tool for assessing PPD, as it has demonstrated good psychometric properties.[6] Postpartum depression (PPD) affects approximately 17% (95% CI, 16 to 18) of women globally, indicating that 1 in every 5 women experiences PPD (95% CI; 16.00 to 18.51).[7] Postpartum depression profoundly impacts the maternal wellbeing and influences offspring outcome as well as family functioning.[8] Immediate postpartum pain has been linked to PPD development, with one study showing that acute postoperative pain severity independently contributes to persistent pain and depression at 8 weeks after Cesarean delivery.[9,10] A recent study also showed that worsened postpartum quality of recovery, including more severe pain, was an independent risk factor for the development of PPD.[11] While the relationship between pain and depression is well-established in patients with chronic pain, fewer data exist on the intersection of PPD and chronic pain in the obstetric population. Preoperative depression is significantly associated with CPSP following CD.[12] Additionally, postoperative depression assessed at four months following CD strongly correlates with CPSP.[13]

In a previously conducted randomized clinical trial, we compared the impact of intrathecal morphine *vs* placebo on CPSP following elective CD.[14] The results showed that administering intrathecal morphine did not effectively reduce the incidence of CPSP at three and six months after CD. In this secondary analysis of the previous trial, our primary objective was to investigate the relationship between provisional diagnosis of PPD at 8 weeks (EPDS scores ≥12) and the incidence of CPSP three and six months post-Cesarean delivery. We hypothesized that the development of PPD at 8 weeks postpartum would be a predictor for the development of CPSP both at three and six months. We also explored the mediating effect of PPD on the relationship between acute severe postoperative pain and CPSP.

METHODS

We conducted a secondary analysis of a previously conducted randomized clinical trial approved by the institutional review committee (IRC) of the BP Koirala Institute of Health Sciences (BPKIHS; Dharan, Nepal) with the IRC number 1183/017. All patients had provided written informed consent before enrolment in the study. The original trial evaluated the effects of intrathecal *morphine vs* placebo on the incidences of CPSP at three and six months after CD and found no significant difference in the incidence of CPSP between parturients who received intrathecal *morphine vs* those who did not, with detailed trial methodology published elsewhere.[14] This secondary analysis study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The study enrolled full-term singleton parturients aged > 18 years, classified as American Society of Anesthesiologists Physical Status II, who were scheduled for planned CD under spinal anesthesia. The exclusion criteria were preeclampsia, height < 150 cm, a body mass index (BMI) > 40 kgm^{-2}, recent opioid use, substance use disorder, significant cardiovascular, renal, or hepatic conditions, known fetal abnormalities, allergies to any study drug, or contraindications to spinal anesthesia. Baseline patient characteristics, such as age, BMI, gestational age, socio-economic status (assessed with Kuppuswamy's scale),[15] previous CD history, and pre-existing chronic pain, were documented. We also recorded preoperative anxiety and depression scores (assessed with the hospital anxiety and depression scale),[16] pain catastrophizing scores,[17] and preoperative pain pressure threshold and tolerance (assessed with a handheld algometer; details of which have been previously reported[14]).

In the trial, 290 patients underwent randomization to receive 100 µg of intrathecal morphine or normal saline as a component of spinal anesthesia. We standardized the perioperative anesthesia and surgical management for all patients. After surgery, we recorded postoperative pain severity at different time points up to 48 hr (using an 11-point numeric rating scale [NRS] score; 0 = no pain and 10 = the worst possible pain), the area of secondary hyperalgesia (in cm^2) around the surgical incision at 48 hr (details explained elsewhere),[14] rescue intravenous morphine (in mg) needed up to 48 hr, and patient satisfaction regarding postoperative analgesia at 48 hr (assessed using a 5-point scale: 1 = highly satisfied, 2 = satisfied, 3 = neutral, 4 = not satisfied, and 5 = strongly dissatisfied).

After discharge from the hospital, we contacted patients via telephone for PPD assessment at 8 weeks and CPSP evaluation at three and six months after surgery. For the provisional diagnosis of PPD, we used the validated Nepali version of the EPDS, which is the most widely used and validated tool for this purpose.[18] The EPDS includes 10 items, each scored from 0–3, resulting in a total score of 0-30. In this study, we identified the presence of PPD with EPDS scores of 12 or higher, as this cutoff point in the Nepalese version of the EPDS demonstrated an accuracy of 98.2%.[18] Chronic postsurgical pain is defined by the presence of 3 criteria: pain at the incision site that developed following surgery, pain that persists for

at least three months, and pain that differs from any pre-existing pain conditions present before the surgery.[1]

The primary outcome of the original study was the incidence of CPSP at three months after surgery, with the secondary outcome being the occurrence of CPSP at six months post-CD. In the present study, we aimed to test the hypothesis that participants reporting EPDS scores ≥ 12, indicating a provisional diagnosis of PPD at 8 weeks, would have a higher likelihood of experiencing CPSP at three and six months after surgery than those with lower EPDS scores. The sample size was based on the data available from our previous study.

Statistical analysis

We used the Shapiro–Wilk test to evaluate the normality of the continuous variables. We expressed all continuous data that were normally distributed as mean (standard deviation [SD]) and analysed the data using two-tailed independent Student's *t* tests; we expressed all non-normally distributed data as median [interquartile range (IQR)] and analyzed the data using Mann–Whitney *U* tests. We used Chi-square tests for categorical variables and applied Fisher's exact tests when the expected cell counts were < 5.

We conducted logistic regression analyses to identify the associations between PPD and CPSP. For building the multivariable regression model, we included variables on the basis of existing knowledge and clinical judgment. We report the results as odds ratios (ORs), with corresponding 95% CIs. We evaluated the goodness of fit of the logistic regression models for the multivariable analysis using the Hosmer–Lemeshow test. We assessed collinearity among the covariates using the variance inflation factor (VIF), with variables exceeding a VIF > 5 regarded as collinear and consequently excluded from the regression model. We also investigated the mediating role of PPD (a binary variable) in the relationship between acute severe postoperative pain (a binary variable) and CPSP (a binary outcome), as illustrated in Fig. 1. To test our hypothesis, we conducted a statistical causal mediation analysis, both with and without adding other covariates (confounders), using the "mediate" package in STATA® version 18 (StataCorp. LP, College Station, TX, USA). This analysis estimates the total effect of acute severe postoperative pain on CPSP and decomposes it into direct and indirect effects (via a mediator) on the odds-ratio scale. We deemed all *P* values < 0.05 were deemed statistically significant. Data were analyzed using Stata 18.0 software.

Fig. 1. Outline of causal mediation analysis model

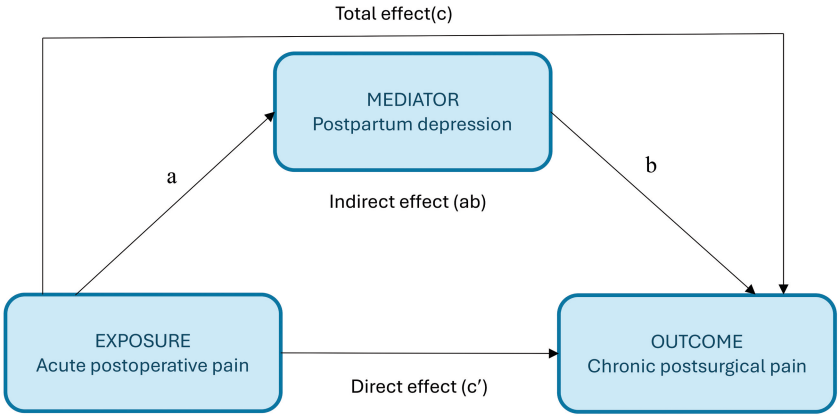
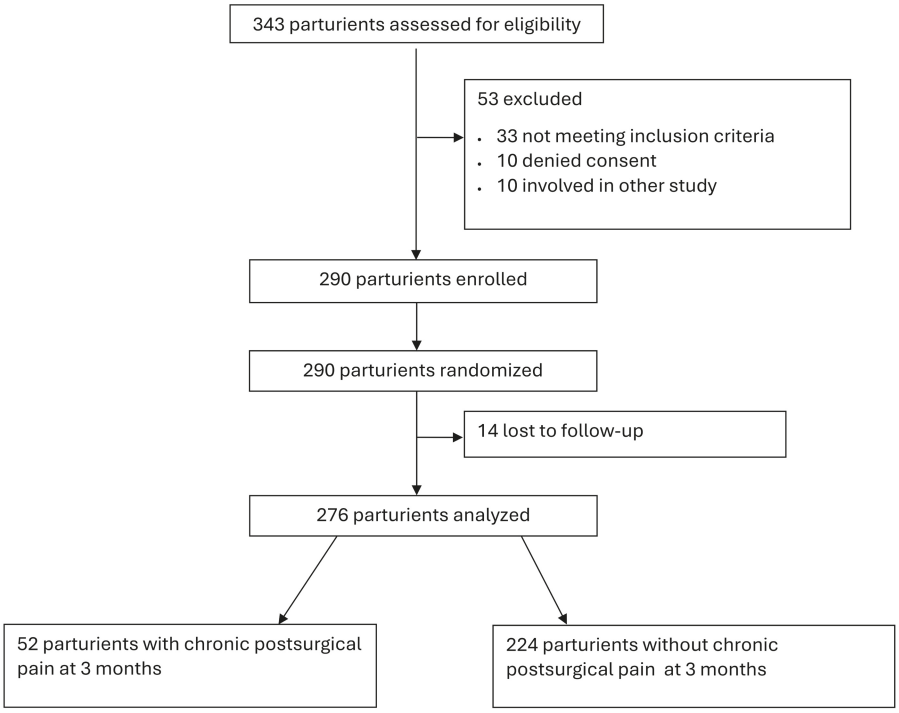


Fig. 2. Flowchart of the study



RESULTS

Of the 290 patients initially randomized in the original study, we included 276 in the final analysis, as 14 patients (5%) were lost to telephone follow-up (Fig. 2). At the 8-week follow-up after surgery, 20 patients (7%) reported a provisional diagnosis of PPD according to EPDS scores. Out of 276 women, 52 (18%) reported chronic postsurgical pain (CPSP) at three months following Cesarean delivery, while 42 (15%) experienced it at six months. Table 1 presents the baseline and clinical characteristics of patients who developed PPD and those who did not. Forty-three out of 256 patients (17%) in the non-PPD group and 9/20 patients (45%) in the PPD group reported CPSP at three months (P = 0.002) (Table 1). Likewise, within the PPD group, 8/20 patients (40%) reported CPSP at 6 months, while in the nonPPD group, 34/256 patients (13%) experienced CPSP (P = 0.001) (Table 1).

Table 1. Baseline patient characteristics and perioperative profiles

Variable	All patients (N=276)	PPD group (N=20)	Non-PPD group (N=256)	*P*-value
Age (yr), mean (SD)	28.2 (4.8)	26.8 (4.8)	28.3 (4.7)	0.16*
Body mass index (kg. m-2), mean (SD)	27.4 (3.6)	26.8 (3.2)	27.4 (3.7)	0.48*
Gestational age (weeks), mean (SD)	38.7 (1.2)	39 (1.2)	38.7 (1.2)	0.36*
Indo-Aryan origin, n/total N (%)	167/276(61%)	14/20 (70%)	153/256 (60%)	0.36**
Previous cesarean delivery, n/total N (%)	185/276 (67%)	15/20 (75%)	170/256 (66%)	0.43**
Pre-existing chronic pain, n/total N (%)	6/276 (2%)	2/20 (10%)	4/256 (1%)	0.06***
Socio-economic status, n/total N (%)				0.55***
Upper class	18/276 (7%)	2/20 (10%)	16/256 (6%)	
Upper middle class	131/276 (47%)	7/20 (35%)	124/256 (49%)	
Lower middle class	82/276 (30%)	7/20 (35%)	75/256 (29%)	
Upper lower class	45/276 (16%)	4/20 (20%)	41/256 (16%)	
HADS scores (0-21)				
Anxiety, median [IQR]	4 [3-6]	5 [4-6]	4 [3-6]	0.25****
Depression, median [IQR]	3 [2-5]	4 [2-5]	3 [2-5]	0.91****
Pain catastrophizing scores, median [IQR]	8 [5-12]	7 [5-9]	8 [5-12]	0.32****
Pain pressure threshold (kg), mean (SD)	4.3 (1.2)	4.5 (1.2)	4.3 (1.2)	0.46*
Pain pressure tolerance (kg), mean (SD)	6.6 (1.4)	6.8 (1.1)	6.6 (1.4)	0.71*
Received spinal morphine, n/total N (%)	139/276 (50%)	7/20 (35%)	132/256 (51%)	0.15**
Duration of surgery (min), mean (SD)	56 (14)	58.7 (14.6)	56.4 (14.1)	0.49*
Severe pain up to 48 h (NRS scores ≥ 7), n/total N (%)	29/276 (11%)	3/20 (15%)	26/256 (10%)	0.45***

Table 1. Continued

Variable	All patients (N=276)	PPD group (N=20)	Non-PPD group (N=256)	P-value
Secondary hyperalgesia at 48 h (cm2), median [IQR]	42.5 [18-76]	68 [21-115]	42 [18-74]	0.14****
IV morphine used up to 48 h (mg), median [IQR]	6 [4-8]	7 [4-10]	6 [4-8]	0.60****
Satisfaction, post-operative analgesia, n/ total N (%)				0.08***
Highly satisfied	36/276 (13%)	3/20 (15%)	33/256 (13%)	
Satisfied	158/276 (57%)	7/20 (35%)	151/256 (59%)	
Neutral	63/276 (23%)	7/20 (35%)	56/256 (22%)	
Dissatisfied	14/276 (5%)	3/20 (15%)	11/256 (4%)	
Strongly dissatisfied	5/276 (2%)	0/20 (0%)	5/256 (2%)	
CPSP, after 3 months, n/total N (%)	52/276 (19%)	9/20 (45%)	43/256 (17%)	0.002**
CPSP, after 6 months, n/total N (%)	42/276 (15%)	8/20 (40%)	34/256 (13%)	0.001**

Abbreviations: CPSP, Chronic postsurgical pain; HADS, Hospital anxiety and depression scale; IQR, interquartile range; NRS, Numeric rating pain scale scores; PPD, Postpartum depression; SD, standard deviation
*Student's *t* test
**Chi square test
***Fisher's exact test
****Mann-Whitney *U* test

The only statistically significant univariable predictor for CPSP after three months was the presence of PPD (OR, 4.05; 95% CI, 1.58 to 10.4; $P = 0.004$) (Table 2). In the multivariable analysis, patients who developed PPD had higher odds of developing CPSP after three months than patients who did not develop PPD (OR, 4.24; 95% CI, 1.53 to 11.7; $P = 0.005$) (Table 2). At six months following surgery, in the univariable analysis the odds of experiencing CPSP was increased by 4.3 times in patients with PPD (OR, 4.35; 95% CI, 1.65 to 11.4; $P = 0.003$) (Table 3). Likewise, an increased requirement of intravenous morphine within the initial 48 hr postoperatively was associated with a statistically significant increased risk of CPSP at 6 months (OR, 1.15; 95% CI, 1.01 to 1.32; $P = 0.03$). Nevertheless, after adjustment for confounding factors in the multivariable logistic regression model, only the presence of PPD was independently associated with a higher risk of CPSP (OR, 4.05; 95% CI, 1.42 to 11.54; $P = 0.009$) (Table 3).

Table 2. Univariable and multivariable analysis of risk factors associated with chronic post-surgical pain after 3 months.

Variable	Univariable		Multivariable	
	OR (95% CI)	***P*-value**	**OR (95%CI)**	***P*-value**
Previous cesarean section	0.60 (0.32 to 1.12)	0.11	0.56 (0.29 to 1.07)	0.08
Preexisting chronic pain	2.20(0.39 to12.34)	0.37	1.40 (0.21 to 9.22)	0.72
Preoperative HADS anxiety scores	0.95 (0.83 to 1.08)	0.46	0.90 (0.77 to 1.06)	0.23
Preoperative HADS depression scores	0.99 (0.86 to 1.13)	0.88	1.03 (0.88 to 1.21)	0.68
Preoperative PCS scores	1 (0.95 to1.04)	0.94	1.01 (0.96 to 1.07)	0.49
Secondary hyperalgesia at 48 h (cm^2)	1 (0.99 to 1.01)	0.1	1 (0.99 to 1.01)	0.21
Severe pain up to 48 h (NRS ≥ 7)	2.13 (0.91 to 5)	0.08	1.85 (0.72 to 4.77)	0.19
IV morphine used up to 48 h (mg)	1.09 (0.96 to 1.23)	0.14	1.06 (0.93 to 1.21)	0.33
EPDS scores ≥ 12	4.05(1.58 to10.37)	0.004	4.24 (1.53 to 11.74)	0.005

Abbreviations: CI, confidence interval; EPDS, Edinburgh postnatal depression scale; HADS, hospital anxiety and depression scale; IV, intravenous; NRS, numeric rating scale; OR, odds ratio; PCS, pain catastrophizing scale

Table 3. Univariable and multivariable analysis of risk factors associated with chronic post-surgical pain after 6 months.

Variable	Univariable		Multivariable	
	OR (95% CI)	***P*-value**	**OR (95%CI)**	***P*-value**
Previous cesarean delivery	0.86 (0.43 to 1.72)	0.68	0.85 (0.41 to 1.76)	0.66
Preexisting chronic pain	2.87(0.50 to 16.22)	0.23	2.05 (0.31 to 13.35)	0.45
Preoperative HADS anxiety scores	0.93 (0.80 to 1.08)	0.36	0.86 (0.73 to 1.02)	0.08
Preoperative HADS depression scores	0.96 (0.83 to 1.12)	0.65	1.01 (0.85 to 1.20)	0.88
Preoperative PCS scores	0.98 (0.93 to 1.04)	0.62	1 (0.94 to 1.07)	0.8
Severe pain up to 48 h (NRS ≥ 7)	1.92 (0.76 to 4.84)	0.16	1.37 (0.49 to 3.80)	0.53
Secondary hyperalgesia at 48 h (cm^2)	1 (0.99 to 1.01)	0.11	1(0.99 to 1.01)	0.2
IV morphine used up to 48 h (mg)	1.15 (1.01 to 1.32)	0.03	1.14 (0.99 to 1.32)	0.05
EPDS scores ≥ 12	4.35 (1.65 to 11.42)	0.003	4.05 (1.42 to 11.54)	0.009

Abbreviations: CI, confidence interval; EPDS, Edinburgh postnatal depression scale; HADS, hospital anxiety and depression scale; IV, intravenous; NRS, numeric rating scale; OR, odds ratio; PCS, pain catastrophizing scale

We did not observe any collinearity among the covariates before inclusion in the multivariable models for CPSP at three and at six months following CD. The multivariable models for CPSP at three and six months had a Hosmer–Lemeshow goodness-of-fit statistic test with $P = 0.15$ and $P = 0.69$, respectively. Table 4 presents the mediation effect of PPD on CPSP. The results indicate that both the direct impact of acute severe postoperative pain and the indirect effect via PPD on CPSP were statistically insignificant.

DISCUSSION

In this secondary analysis of a previously reported randomized trial, we explored several peri- and postpartum patient characteristics aiming to identify those at heightened risk for CPSP following elective CD. Our findings show that a provisional diagnosis of PPD at 8 weeks after CD was strongly associated with CPSP at three and six months.

Chronic postsurgical pain after CD is not infrequent, with a reported incidence ranging from 7% to 30%.[4] A recent meta-analysis and a narrative review highlighted the presence of the preoperative pain and the severity of acute postoperative pain as factors associated with CPSP following CD.[3,4] In contrast, the link between pre-existing psychological vulnerability—i.e., the presence of anxiety, depression, or catastrophizing—with CPSP following CD was inconsistent. One study found that preoperative depression assessed with the EPDS scale was a reliable predictor for chronic pain at three months and at six months after CD.[12] Nevertheless, the studies on CPSP that have explored the risk factors after CD are limited to the early postoperative period.[3,4] Because the transition from acute to chronic pain may be influenced by postsurgical psychological factors it is necessary to identify these modifiable variables beyond the healing phase of the wound scar. In this context, PPD may be a significant contributing factor influencing the occurrence of CPSP.

The mechanisms by which depression increases the risk of chronic pain are not fully understood. One proposed explanation is that depression leads to the depletion of serotonin and norepinephrine in the central nervous system.[19] This depletion alters the descending modulatory pathways, resulting in the amplification of pain. Studies in nonobstetric populations have shown the ability of pre-existing depression to predict the development of chronic pain.[20,21] Nevertheless, we did not find a significant association between pre-existing depression before surgery and CPSP. Since depression and chronic pain share common neuroplastic changes, their interaction is often bidirectional, suggesting that persistent pain may plausibly contribute to depression. Nevertheless, we did not evaluate subacute postpartum pain, such as pain at 2- or 4-weeks following CD. Therefore, our findings only show an association between PPD and CPSP, without establishing causality. A longitudinal assessment of pain trajectories and depression throughout the perinatal period would provide a more comprehensive understanding of the interaction between depression and persistent pain. A key strength of our study was the assessment of the mediating role of PPD in the relationship between acute severe postoperative pain and CPSP. Nevertheless,

the indirect effect was insignificant, indicating that the ability of PPD to predict CPSP was not driven by an association with greater pain intensity in the immediate postoperative period.

Table 4. Total, direct, and indirect association of acute severe postoperative pain with chronic postsurgical pain mediated through postpartum depression.

Effect	Estimates OR (95% CI)	P value	Proportion mediated % (95% CI)
CPSP at 3 months			
Model without confounders			0.08 (-0.18 to 0.34)
Direct effect	2.02 (0.91 to 4.49)	0.08	
Indirect effect	1.05 (0.87 to 1.27)	0.57	
Total effect	2.13 (0.91 to 5)	0.08	
Model with confounders*			0.10 (-0.22 to 0.40)
Direct effect	1.78 (0.75 to 4.23)	0.18	
Indirect effect	1.05 (0.87 to 1.28)	0.57	
Total effect	1.88 (0.75 to 4.71)	0.17	
CPSP at 6 months			
Model without confounders			0.16 (-0.38 to 0.71)
Direct effect	1.75 (0.70 to 4.35)	0.22	
Indirect effect	1.09 (0.79 to 1.51)	0.57	
Total effect	1.92 (0.76 to 4.84)	0.16	
Model with confounders*			0.27 (-0.73 to 1.28)
Direct effect	1.33 (0.51 to 3.42)	0.54	
Indirect effect	1.10 (0.77 to 1.56)	0.58	
Total effect	1.47 (0.56 to 3.84)	0.43	

Abbreviations: CI, confidence interval; CPSP, chronic postsurgical pain; OR, odds ratio
**Adjusted for previous Cesarean delivery, pre-existing chronic pain, preoperative anxiety, depression and pain catastrophizing, secondary hyperalgesia, postoperative intravenous morphine up to 48 hr.*

A systematic review has highlighted the potential negative effects of maternal PPD on both maternal and child health.[22] Among the consequences of untreated maternal PPD are a diminished quality of life, heightened risk behaviours, and disruptions in social relationships. Interestingly, a few studies have explored the relationship between depression and the presence of chronic pain conditions, such as pelvic pain disorders and dyspareunia, in nonpregnant populations.[23-25] Nevertheless, research on the association between PPD and CPSP remains scarce. A prospective cohort study found a significant correlation between PPD and CPSP at four months following CD.[13] However, the simultaneous assessment of

PPD and CPSP within the same timeframe in that study suggests a bidirectional relationship, making it challenging to establish causation.

Postpartum depression is one of the most common mental disorders of pregnancy. While maternal care primarily emphasizes pregnancy and the early postpartum period, the psychological wellness of mothers in later phases should not be overlooked, as the recent MBRRACE-report covering 2018-2020 identified that mental health-related causes were responsible for nearly 40% of maternal deaths occurring within the first year after pregnancy in the UK.[26] Early identification of PPD holds the potential for implementing psychosocial interventions that could mitigate the severity and consequences of PPD. Indirectly, this may also contribute to a reduction in the incidence of CPSP. Hence, there is a crucial need for future prospective studies to investigate whether preventing or treating PPD in the early postpartum phase can, apart from improving maternal health, diminish the occurrence of CPSP.

It is intriguing that in our univariable analysis, we found a significant correlation between postoperative opioid requirements and the likelihood of CPSP after six months following CD. Nevertheless, after accounting for confounding factors, this association became insignificant. Current evidence has been increasingly highlighting the link between perioperative opioid consumption and CPSP. Studies have elucidated that preoperative chronic opioid usage is associated with a higher incidence of CPSP.[27,28] The probable explanation lies in the neuroadaptive changes that occur owing to chronic opioid administration, leading to allodynia and hyperalgesia.[29] The question of whether acute or excessive use of opioids in the early postoperative period contributes to the development of CPSP remains a topic of debate. Notably, a study found that high-dose remifentanil infusions during cardiac surgery were linked to chronic thoracic pain 1 year after sternotomy.[30] In contrast, a retrospective cohort study reported that increased intraoperative opioid doses were associated with lower incidences of CPSP at three months.[31] The higher opioid requirement in the intraoperative and postoperative period may be attributed to either the intense pain experienced or opioid-induced hyperalgesia (OIH). Given that both the worsening of acute postoperative pain and OIH following surgery are risk factors for CPSP, it becomes crucial to differentiate between these two entities. Consequently, there is a need for further, larger trials with robust methodologies to thoroughly explore the relationship between perioperative opioids and CPSP.

A narrative review in 2020 reported that patients with pre-existing chronic pain are at an increased risk of developing CPSP after CD.[4] Nevertheless, some studies have not observed preoperative pain as a significant risk factor for CPSP following CD.[12,13,32] In our study, although the odds of developing CPSP were higher in patients with preoperative chronic pain, the association was not statistically significant. One possible reason for this finding could be the small number of patients with pre-existing chronic pain included in our study.

LIMITATIONS

This study has several limitations. First, this study was a secondary analysis of previously published study; therefore, the sample size and statistical power were not specifically calculated. It has been argued that *post-hoc* power calculations can be misleading and flawed, particularly in retrospective studies where additional data cannot be collected. [33] Therefore, given the *post-hoc* nature of our study, the results should be interpreted with caution. Second, the rate of PPD in our study was lower than the 17% reported in a previous study conducted in Nepal,[18] which might be the result of follow-up data being collected by phone and cultural stigma surrounding mental health. In our setting, telephone-based screening was feasible as most participants were unlikely to attend follow-up visits in person. Moreover, a study has shown that EPDS, when administered via telephone, retains its psychometric properties.[34] Nonetheless, the small number of patients with PPD may limit the generalizability of our findings. Therefore, a larger cohort with better representation of patients experiencing PPD would strengthen the robustness of our study's findings. Lastly, our primary focus was solely on persistent wound pain, and we did not assess other sources of persistent painful postpartum conditions (such as back pain, pelvic pain, or persistent headache) which might be associated with PPD. In addition, pre-existing depression was assessed using the HADS rather than the EPDS, which may have led to inconsistencies in reporting pre-existing depression. Likewise, we did not specify if patients received any treatment for depression before delivery or after the diagnosis of PPD.

CONCLUSION

In this secondary analysis of a previous randomized trial, we found that a provisional PPD diagnosis at 8 weeks was associated with an increased risk of CPSP at three and six months after CD. Further research is warranted to explore the dynamic relationship between PPD and the development of CPSP following CD.

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Chapter 5

Preoperative higher depression scores are associated with risk of hypotension following spinal anesthesia for cesarean delivery

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ABSTRACT

Objective

During pregnancy, depression is linked to altered autonomic functions, including reduced heart rate variability. Reduced heart rate variability is associated with an increased risk of hypotensive episodes following spinal anesthesia for cesarean delivery (CD). This study aimed to evaluate whether antenatal depression is associated with post-spinal hypotension during CD.

Methods

This secondary analysis utilized data from a previously conducted trial involving 290 full-term singleton pregnant women with American Society of Anesthesiologists (ASA) physical status II, undergoing elective CD under spinal anesthesia. Patients were randomized to receive either 100 μg of intrathecal morphine or normal saline, in addition to the standard spinal mixture of 0.5% bupivacaine (2.2 mL) with 10 μg fentanyl. The primary outcome of the present study was the incidence of post-spinal hypotension, defined as systolic blood pressure <80% of baseline. We performed multivariable logistic regression to examine the association between antenatal depression scores (assessed with Hospital Anxiety and Depression Scale) and post-spinal hypotension.

Results

Of the 290 participants, 164 (56%) developed post-spinal hypotension. The median (interquartile range) antenatal depression scores were higher in the hypotensive group compared with the nonhypotensive group (4 [3 to 5] vs. 3 [2 to 4], p = 0.003). Multivariable logistic regression revealed that higher depression scores (OR = 1.15, 95% CI 1.009–1.31, p = 0.036) and sensory block height ≥ T4 (OR = 1.84, 95% CI = 1.03–3.30, p = 0.039) were significantly associated with post-spinal hypotension.

Conclusion

Higher antenatal depression scores are associated with an increased risk of post-spinal hypotension in women undergoing elective CD.

INTRODUCTION

Cesarean delivery (CD) is most often performed under spinal anesthesia (SA); however, hypotension is a common complication that typically manifests within minutes of SA administration. This so-called post-spinal hypotension affects approximately one-third of patients despite routine prophylactic measures.[1] Adverse effects of post-spinal hypotension include maternal dizziness, nausea, and vomiting during the CD, as well as an increased risk of fetal acidosis.[2] These complications may negatively impact the maternal experience during childbirth, hinder recovery, and affect neonatal well-being, emphasizing the importance of accurately predicting and preventing this undesirable complication during CD.[2]

The autonomic nervous system (ANS), along with the cardiovascular and endocrine systems, plays a crucial role in regulating blood pressure during pregnancy.[3] Heart rate variability (HRV) is a key marker of ANS activity and physiological resilience during pregnancy, and it reflects the balance between parasympathetic and sympathetic functions.[3] Reduced HRV, alongside increased baseline sympathetic tone, signifies an ANS imbalance that can affect blood pressure regulation and compromise cardiovascular stability in pregnancy.[4]

Psychiatric disorders, such as depression, can further complicate this regulation, as antenatal depression is associated with alterations in autonomic function, including suppressed HRV.[5,6] In obstetric anesthesia, reduced HRV and elevated baseline sympathetic tone have emerged as predictors of post-spinal hypotension after CD.[7-9] Based on this evidence, we hypothesized that higher preoperative depression scores, indicative of psychological distress and autonomic dysfunction, are predictive of post-spinal hypotension during CD.

METHODS

We previously conducted a randomized clinical trial approved by the Institutional Review Committee of BP Koirala Institute of Health Sciences with the IRC number 1183/017, involving 290 patients undergoing elective CD with SA.[10] All patients had provided written informed consent before enrollment in the study. The aim was to investigate whether intrathecal morphine would reduce the incidence of chronic postsurgical pain. The purpose of this secondary analysis of the previously conducted clinical trial was to assess the relationship between preoperative depression scores and post-spinal hypotension after CD.

The study included full-term singleton pregnant women over 18 years of age with an American Society of Anesthesiologists (ASA) physical status II, defined as patients with a well-controlled disease without substantive functional limitations, scheduled for planned CD under SA. Exclusions were patients with preeclampsia, height < 150 cm, body mass index (BMI) > 40 kg/m^2, recent opioid use, substance abuse history, significant cardiovascular, renal, or hepatic conditions, fetal abnormalities, drug allergies, or contraindications to SA.

Baseline characteristics (age, height, weight, BMI, gestational age, previous CD history, and preexisting chronic pain) were documented along with preoperative anxiety and depression scores (assessed with Hospital Anxiety and Depression Scale), and pain catastrophizing scores, details of which have been previously reported.[10]

Upon arrival at the operating room, standard monitoring (noninvasive blood pressure, electrocardiography, and pulse oximetry) was initiated. Baseline systolic blood pressure (SBP) and heart rate were recorded before SA administration. SA was administered at the L3-L4 or L4-L5 interspace using a 25-G spinal needle. The morphine group received intrathecal hyperbaric bupivacaine 11 mg (2.2 mL 0.5%), fentanyl 10 μg (0.2 mL), and preservative-free morphine 100 μg (0.1 mL). The placebo group received hyperbaric bupivacaine 11 mg (2.2 mL 0.5%), fentanyl 10 μg (0.2 mL), and normal saline (0.1 mL). Patients received IV Ringer lactate solution coloading, 10 mL/kg, and a phenylephrine infusion at 25 μg/min. After spinal injection, patients were positioned supine with a left lateral tilt. Surgery commenced after achieving sensory loss to pinprick sensation at T6 or higher. All patients received intravenous ondansetron 4 mg. Hypotension, defined as SBP <80% of baseline, was treated with phenylephrine or ephedrine at the anesthesiologist's discretion. The primary outcome of this study was the incidence of post-spinal hypotension.

The Shapiro–Wilk test was used to evaluate the normality of the continuous variables. Continuous data with a normal distribution were expressed as mean (SD), while non-normally distributed data were expressed as median (interquartile range). Categorical data were presented as number (percentage). The independent sample *t* tests and the Mann–Whitney *U* test were used to compare normally and non-normally distributed data, respectively, between the hypotensive and nonhypotensive groups. For categorical data, the Pearson χ^2test or Fisher exact test was applied, as appropriate. We conducted univariable and multivariable logistic regression analyses to explore the variables associated with hypotension after SA. Variables for the multivariable logistic regression model were included based on prior research and clinical knowledge: BMI, gestational age, preexisting chronic pain, preoperative pain catastrophizing, anxiety and depression, baseline SBP, baseline heart rate, use of spinal morphine, and maximum sensory block height. The results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CI). All *p*-values < 0.05 were considered statistically significant. Data were analyzed using Stata 15.0 software (StataCorp. LP, College Station, Texas, USA).

TABLE 1. Comparison of Demographic and Perioperative Profiles Between Hypotensive and Nonhypotensive Group

	All patients n=290	Hypotensive group N=164	Non-hypotensive group N=126	*P*-value
Age (y), mean (SD)	28.14 ± 4.86	28.25 ± 4.98	28.01 ± 4.72	0.68*
Weight (kg), mean (SD)	67 ± 9.34	67.08 ± 9.66	66.88 ± 8.93	0.85*
Height (cm), mean (SD)	156.33 ± 5.47	155.90 ± 5.22	156.88 ± 5.76	0.13*
Body mass index (kg/m^2), mean (SD)	27.41 ± 3.68	27.57 ± 3.71	27.21 ± 3.64	0.41*
Gestational age (wk), mean (SD)	38.77 ± 1.22	38.67 ± 1.12	38.89 ± 1.34	0.13*
Indo-Aryan origin, n (%)	174 (60)	95 (58)	79 (63)	0.41***
Previous cesarean delivery, n (%)	194 (67)	111 (68)	83 (66)	0.74***
Pre-existing chronic pain, n (%)	6 (2)	5 (3)	1 (1)	0.23****
HADS scores (0-21)				
Anxiety, median (IQR)	4.5 (3-6)	5 (3-6)	4 (3-6)	0.54**
Depression, median (IQR)	3 (2-5)	4 (3-5)	3 (2-4)	0.003**
Pain catastrophizing scores (0-52), median (IQR)	8 (5-12)	8 (6-12)	7 (5-12)	0.48**
Baseline SBP (mmHg), mean (SD)	119.98 ± 7.18	119.46 ± 6.97	120.66 ± 7.41	0.15*
Baseline HR (beats/min), mean (SD)	82.74 ± 9.97	83.36 ± 10.32	81.92 ± 9.48	0.22*
Received spinal morphine, n (%)	145 (50)	89 (54)	56 (44)	0.097***
IONV, n (%)	11 (4)	8 (5)	3 (2)	0.35****
Shivering, n (%)	19 (7)	11 (7)	8 (6)	0.90***
Bradycardia (HR < 50/min), n (%)	19 (7)	19 (7)	0 (0)	<0.001****
Pruritus, n (%)	8 (3)	6 (4)	2 (2)	0.47****
Sensory block height ≥ T4, n (%)	227 (78)	137 (84)	90 (71)	0.013***
Duration of surgery (min), mean (SD)	56.77 ± 14.31	57.06 ± 13.86	56.41 ± 14.94	0.70*

Abbreviations: BMI, body mass index; CD, cesarean delivery; HADS, Hospital Anxiety and Depression Scale; HR, heart rate; IONV, intraoperative nausea and vomiting; IQR, interquartile range; SBP, systolic blood pressure.

*Independent sample *t* tests.

**Mann-Whitney *U* test.

***Pearson χ2 test.

****Fisher exact test.

RESULTS

Out of 290 patients who completed the study, 164 patients (56%) developed post-spinal hypotension. Patient demographics and the perioperative variables between hypotensive and nonhypotensive group are depicted in table 1. The median (interquartile range) depression scores were 4 (3 to 5) in the hypotensive group and 3 (2 to 4) in the nonhypotensive group (median difference = 1, $p < 0.003$). Univariable logistic regression analysis showed that an increase in depression scores and sensory block height ≥ T4 were associated with post-spinal hypotension (Table 2). Similarly, in multivariable logistic regression analysis, an increase in depression scores (OR = 1.15, 95% CI = 1.009-1.31, $p = 0.036$) and sensory block height ≥ T4 (OR = 1.84, 95% CI 1.03 = 3.30, $p = 0.031$) were significant independent risk factors for post-spinal hypotension (Table 2).

TABLE 2. Univariable and Multivariable Logistic Regression Analysis of Risk Factors Associated With Post-spinal Hypotension

Variable	Univariable		Multivariable	
	OR (95%CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Body mass index (kg/m^2)	1.02 (0.96-1.09)	0.41	1.02 (0.95-1.09)	0.52
Gestational age (wk)	0.86 (0.71-1.04)	0.13	0.83 (0.68-1.02)	0.149
Preoperative depression (HADS scores)	1.12 (1.009-1.26)	0.034	1.15 (1.009-1.31)	0.036
Preoperative anxiety (HADS scores)	1.03 (0.93-1.14)	0.52	1.01 (0.90-1.14)	0.75
Preexisting chronic pain	3.93 (0.45-34)	0.21	3 (0.32-27.6)	0.33
Preoperative pain catastrophizing scores	1 (0.96-1.04)	0.80	0.98 (0.94-1.02)	0.46
Baseline SBP (mmHg)	0.97 (0.94-1.00)	0.15	0.98 (0.95-1.01)	0.38
Baseline HR (beats/min)	1.01 (0.99-1.03)	0.22	1.01 (0.98-1.03)	0.31
Received spinal morphine	1.48 (0.93-2.36)	0.098	1.48 (0.90-2.41)	0.11
Sensory block height				
< T4	1 (ref)		1 (ref)	
≥ T4	2.02 (1.15-3.57)	0.014	1.84 (1.03-3.30)	0.039

Abbreviations: BMI, body mass index; HADS, hospital anxiety and depression scale; HR, heart rate; OR, odds ratio; SBP, systolic blood pressure.

DISCUSSION

To the best of our knowledge, this is the first study to explore the relationship between antenatal depression and post-spinal hypotension. We observed that preoperative higher depression scores were associated with an increased risk of post-spinal hypotension after adjusting for several confounders in the multivariable logistic regression analysis.

The ANS plays an important role in regulating blood pressure during pregnancy. Surrogate markers of altered autonomic functions, such as reduced HRV and increased baseline sympathetic tone, have been predictive of post-spinal hypotension in the obstetric population.[7-9] Similarly, in highly anxious pregnant women, frequent hypotensive episodes have been reported after SA for CD.[11]

One possible explanation is that altered HRV due to anxiety may have played a role in potentiating hypotension because reduced HRV is considered a potential physiological biomarker of anxiety disorders.[12]

Another negative emotional state during pregnancy, that is, antenatal depression, can have long-term detrimental effects on pregnant mothers and their newborns. During a normal pregnancy, ANS activity shifts towards higher basal sympathetic and lower vagal modulation, such as (HRV). Moreover, the ANS is one of the key physiological mechanisms by which an individual reacts to stress response. Consequently, during psychological distress, there is a further reduction of sympathovagal imbalances. Several studies have explored the relationship between autonomic function and maternal depression during pregnancy. The low-frequency/high-frequency ratio as a component of HRV and baroreflex sensitivity was found to be significantly correlated with depression scores in pregnant women.[5,6] These mechanisms may explain, in part, why depression-induced alterations in ANS might have played a role in post-spinal hypotension in our study.

There are a few limitations related to this study. First, although there is a lack of biological plausibility for an association between spinal-induced hypotension and pre-operative depression, further prospective studies are warranted to explore the role of biomarkers of ANS, such as HRV, in women with antenatal depression and their association with post-spinal hypotension following CD. Second, the exclusion of women with preeclampsia from this study limits the generalizability of our findings. Third, we did not document the magnitude of the fall in intraoperative SBP, and the total vasopressor needed. Finally, the study was not powered to investigate the outcome, that is, post-spinal hypotension.

CONCLUSION

Our study showed that preoperative higher depression scores in pregnant women were associated with a significant risk of post-spinal hypotension during CD. We suggest that the effect of antenatal depression on post-spinal hypotension should be assessed in further studies.

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Chapter 6

Effect of height versus height/ weight-based spinal bupivacaine on maternal hemodynamics for elective cesarean in short stature patients: a randomized clinical trial

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ABSTRACT

Purpose

Doses of spinal bupivacaine adjusted to patient height or height/weight have been shown to provide hemodynamic stability during cesarean section. However, their effects in short stature parturients are unknown.

Methods

In this double-blind, randomized clinical trial, we randomly assigned short parturients (height < 150 cm) undergoing elective cesarean section, to receive doses of intrathecal hyperbaric bupivacaine either height or height/weight-adjusted, in a 1:1 ratio. The primary outcome was post-spinal hypotension (defined as systolic blood pressure [SBP] <90% of baseline between spinal administration and delivery of the baby). Secondary outcomes included severe post-spinal hypotension (SBP < 80% of baseline), post-delivery hypotension (SBP < 90% and < 80% of baseline), intraoperative bradycardia, nausea and vomiting, shivering, rescue analgesic needed, and spinal block characteristics.

Results

A total of 112 patients underwent randomization. Post-spinal hypotension (SBP < 90% of baseline) occurred in 52% of the patients in the height/weight group and in 55% in the height group (difference − 3.5%: 95% confidence interval [CI] − 22 to 14.8, $P = 0.705$). There was no significant difference between the two groups in the occurrences of post-spinal severe hypotension (SBP < 80% of baseline), post-delivery hypotension, and spinal block characteristics. Six patients (11%) in the height/weight group needed intraoperative rescue analgesic compared to none in the height group ($P = 0.027$).

Conclusion

We found that height-based dosing in short parturients provides the optimal trade-off between intraoperative hemodynamic instability and provision of pain-free anesthesia.

INTRODUCTION

The most common side effect of spinal anesthesia in women undergoing cesarean section is hypotension, which occurs in more than two-thirds of patients if no prophylactic measures are taken [1]. If this hypotension is not prevented nor treated immediately, it may cause maternal nausea, vomiting, dizziness, and reduced consciousness; it can also impair uteroplacental perfusion, which may result in fetal bradycardia, depressed Apgar scores and fetal acidosis [2]. To prevent or treat hypotension, several strategies have been extensively studied, such as reducing the dose of intrathecal local anesthetic (LA), co-loading with intravenous fluids, vasopressors, and appropriate positioning of the mother [3, 4].

The dose of intrathecal local anesthetic is the main factor determining the balance between a successful block and the occurrence of maternal hypotension. The ED95 of intrathecal bupivacaine to achieve successful anesthesia, when co-administered with intrathecal opioids, ranges from 11 to 12.6 mg [5, 6]. As maternal hypotension and nausea/vomiting still occur at these recommended doses, several investigators have explored the effectiveness of lower doses of bupivacaine. Lowering the dose of intrathecal bupivacaine provides better maternal hemodynamic stability, but it may compromise the quality of anesthesia. Moreover, there is no consensus regarding the cut-off at which the dose is defined as low [6].

Studies have demonstrated that tailoring doses of LA for spinal anesthesia to maternal weight and height or height-based regimens can decrease the risk of hypotension while producing similar anesthesia quality compared to fixed conventional doses [7-9]. Adjusting the doses of LA based on body habitus could limit the maximum cephalad spread using smaller doses in the tailored regimen, which is less than the fixed regimen. Further, the intrathecal bupivacaine doses based on height and weight tends to be lower than doses based on height alone [7, 8]; as a result, hypotensive events are more likely to occur in height-based regimen. In a comparison between height-based dosing and height/weight-based dosing, the height-based dosing group had a significantly higher occurrence of hypotension, even though there were no significant differences in the dosages of bupivacaine [10]. The lower mean height of patients in the height-based dosing group in comparison to the height/weight-based dosing group may have contributed to the higher incidence of hypotension seen in the former group [10]. Nonetheless, these studies were conducted in parturients with normal ranges of height, and the effectiveness of these dosing schemes in short-statured parturients remains unexplored.

Therefore, the present randomized trial was designed to compare the hemodynamic effects and effective anesthesia of two dosing regimen of intrathecal bupivacaine for CS in short stature patients based on height versus height/weight. Our hypothesis was that administering spinal bupivacaine doses based on both height and weight, as determined by Harten et al. [8], would result in a lower incidence of hypotension in short stature patients, compared to those who receive doses based on height alone.

METHODS

This randomized double-blind clinical trial was conducted at BP Koirala Institute of Health Sciences (BPKIHS) from November 2019 to September 2021. This study was approved by the BPKIHS Institutional Review Committee (IRC no. IRC/11525/019) and the Nepal Health Research Council Ethical Review Board (ERB protocol no. 630/2019). The written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04082676, Principal investigator: Asish Subedi, https://clinicaltrials.gov/ct2/show/NCT04082676, Date of registration: September 9, 2019). The trial was conducted in accordance with the principles of the 1964 Declaration of Helsinki and adheres to the applicable CONSORT guidelines. Patients were screened for eligibility by the investigators the night before surgery, during the pre-anesthetic visit at the in-patient unit. During this visit, patients were educated regarding the use of numeric rating scale (NRS) scores and written informed consent was obtained. Preoperative anxiety was recorded in NRS scores, with 0 = no anxiety and 10 = maximum anxiety, as reported by the patient.

Eligible subjects were full-term singleton parturients with height < 150 cm of American Society of Anesthesiologists physical status II, scheduled for elective cesarean section under spinal anesthesia. Patients with height < 140 cm, hypertensive disorders, placental disorders, body mass index ≥ 40 kg/m^2, endocrine or hormonal disorders, cardiovascular, cerebrovascular, or renal diseases, polyhydramnios or a known history of obstetric morbidity or fetal abnormalities and baseline systolic blood pressure (SBP) less than 100 mmHg were excluded from the study. The enrolled patients were randomly assigned to 2 equal groups (allocation ratio 1:1) according to an online generated randomization list (https://www.sealedenvelope.com), using the variable block sizes of 4, 6 and 8. An independent researcher created the trial-group assignment and concealed the group allocation in sequentially numbered, sealed opaque envelopes. On the day of surgery, each secured envelope was handed over to the anesthesia assistant who prepared the drug mixture for spinal anesthesia according to the group allocation. In one group, the dose of hyperbaric bupivacaine 0.5% was calculated from the chart provided by Harten and colleagues (Table 1) based on height/weight [8]; while in the other group, the dose was based on patients' height (0.06 mg/cm) [7]. Fentanyl (10 µg) was added to the bupivacaine in both groups.

Patients fasted for at least 8 h and received ranitidine 50 mg and metoclopramide 10 mg intravenously via an 18-gauge cannula before transfer to the operation room. The patient was positioned on the operating table with a 15° wedge under the right buttock and standard monitoring (electrocardiography, pulse oximetry, and noninvasive blood pressure) was applied. Three successive readings of heart rate (HR) and systolic blood pressure (SBP) were taken at 2-min intervals. The averages of these recordings were documented as baseline parameters.

The subarachnoid block was performed by the attending anesthesiologist in the sitting position at the L3-L4 or L4-L5 vertebral interspace using a 25-gauge Quincke spinal needle via the midline approach. The study solution was administered according to the group allocated. The patient was immediately repositioned supine, with the 15° wedge in place. Immediately after spinal injection, patients received 1L of Ringer's lactate as co-loading over 10-15 min, using a pressurizer bag. Patients, attending anesthesiologists, and the investigator who collected the data and assessed the outcomes were blinded to the study group allocation.

Table 1 Height/weight-based dosing regimen of 0.5% hyperbaric bupivacaine for spinal anesthesia for cesarean section [8]

Patient weight (kg)	Patient height (cm)								
	140	145	150	155	160	165	170	175	180
50	1.5	1.7	1.8	1.9					
55	1.5	1.6	1.8	1.9	2				
60	1.4	1.6	1.7	1.8	2	2.1			
65	1.4	1.5	1.7	1.8	1.9	2.1	2.2		
70	1.3	1.5	1.6	1.8	1.9	2	2.2	2.3	
75		1.4	1.6	1.7	1.9	2	2.1	2.3	2.4
80		1.4	1.5	1.7	1.8	2	2.1	2.2	2.4
85			1.5	1.6	1.8	1.9	2.1	2.2	2.3
90			1.4	1.6	1.7	1.9	2	2.2	2.3
95				1.5	1.7	1.8	2	2.1	2.3
100				1.5	1.7	1.8	1.9	2.1	2.2
105					1.6	1.7	1.9	2	2.2
110						1.7	1.8	2	2.2

Values are in milliliters

Immediately after spinal injection, sensory levels were assessed bilaterally at the anterior axillary line with a cotton swab soaked with ethyl chloride. The block level was checked every min for the first 10 min, and the maximum level attained was registered. Surgery was allowed to commence once the sensory loss reached a level of T6 or higher, bilaterally. If the sensory block level did not reach T6 within 10 min, patients were placed in 15° Trendelenburg position. If the sensory block height was still below T6, the procedure was considered a failed spinal and the patient received general anesthesia. Motor block was assessed every min, for 10 min after injection, using the Bromage motor blockade scale scores [11].

SBP was recorded every minute for the first 10 min, every 2.5 min for the next 10 min, and then every 5 min till the end of surgery. Post-spinal hypotension (time from spinal injection

to delivery) was defined as a SBP < 90% of baseline and severe post-spinal hypotension was defined as a SBP < 80% of baseline. Post-delivery hypotension (time from delivery of the baby to end of surgery) was defined as a SBP < 90% of baseline and severe post-delivery hypotension was defined as a SBP < 80% of baseline. SBP's < 90% and < 80% of baseline were treated with bolus injections of phenylephrine 50 µg and 100 µg, respectively. Also, Ringers lactate was administered rapidly when hypotension occurred. Hypotension associated with bradycardia (HR < 50 beats/min) was treated with IV ephedrine 6 mg followed by IV atropine 0.5 mg.

Intravenous fentanyl 20 µg was administered if a patient reported intraoperative pain, and this dose was repeated when necessary. In case of persisting pain, IV ketamine 0.25 mg/kg was given. All patients received IV ondansetron 4 mg. Patients were instructed to report intraoperative nausea based on an 11-point NRS, where 0 describes "no nausea" and 10 describes nausea "as worst as it could be". NRS > 0 was considered as nausea; patients reporting the NRS score ≥ 5 for nausea and/or vomiting were managed with IV dexamethasone 4 mg. Occurrence of intraoperative pruritus, shivering (based on grading described previously) [12], and dizziness was recorded. All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation and one cotton blanket over the entire body after the operation. The operating room temperature was maintained at 23-25 °C. IV fluids were administered at room temperature. The volume of intraoperative IV fluids used and the estimated blood loss were recorded for each patient. Supplemental oxygen was administered at a rate of 5 L/min through a face mask during the operation. Intraoperative pruritus was assessed using the NRS scale (0-10 scale, with 0 = no pruritus, and 10 = worst pruritus imaginable), with a NRS score ≥ 4 was treated with IV chlorpheniramine 10 mg.

Oxytocin 2 U was administered IV over 5-10 s after delivery of the baby, followed by a maintenance infusion of 10 u/h (oxytocin 20 u in 500 ml of Hartmann's solution). Quality of anesthesia was assessed using a four-point scale: 1 =excellent; 2 = good: some feelings but no discomfort; 3 =fair: some discomfort but rescue analgesia unnecessary; and 4 = poor: major discomfort which required rescue analgesia. Surgeons were asked to grade operating conditions as "very good", "good" or "poor." Neonatal Apgar scores were recorded at 1 and 5 min after delivery by the attending pediatrician. Bupivacaine 0.25% (30 ml) was infiltrated subcutaneously after closure of the skin incision. At the end of surgery, sensory and motor block levels were assessed using the absence of touch and the Bromage scale at 10-min intervals, until the sensory block level had regressed to T10 and the motor block had recovered to a Bromage scale score of 0. Patient satisfaction with intraoperative anesthesia for cesarean section was recorded before discharge from PACU, using NRS scores with 0 = "very dissatisfied" and 10 ="very satisfied". Duration of the pain-free period was defined as the time (h) between the intrathecal injection and the first perception of pain. Postoperative analgesia was administered at the discretion of the attending obstetrician.

The primary outcome was the incidence of post-spinal hypotension. Secondary outcomes were frequencies of severe post-spinal hypotension, post-delivery hypotension, severe post-delivery hypotension, bradycardia, nausea, vomiting, pruritus, shivering, dizziness, need for supplemental intraoperative analgesic, post-spinal sensory and motor block characteristics, quality of anesthesia, patient satisfaction with anesthesia, and neonatal Apgar scores at 1 and 5 min after delivery.

Sample size calculation

A previous study reported the incidence of hypotension as 57% and 27% in parturients receiving IT bupivacaine based on height-based versus height/weight-based regimens, respectively [10]. To detect a difference of 30% in the incidence of post-spinal hypotension, we needed 48 subjects in each group with a power of 80% and using a two-tailed alpha of 0.05 (STATA version 15.1, STATA Corp., TX). Assuming a 15% attrition rate, we enrolled 112 patients (56 in each group).

Statistical analysis

Normality of the continuous data was assessed using histograms and the Shapiro-Wilk test. The mean (standard deviation) was used for normally distributed variables and the median (interquartile range) for data that were not normally distributed. For categorical variables, number (percentage) was used. The Student's unpaired t tests and the Mann-Whitney U tests were applied for continuous data which showed normal and skewed distribution, respectively. For categorical variables, the Chi-square test was used, and otherwise the Fisher exact test was used if the expected values in any of the cells of a contingency table were less than 5. For comparison of the incidence of hypotension, we used between-group differences in percentage points with a corresponding 95% confidence interval. A two-sided *P*-value < 0.05 was considered as statistically significant. Statistical analysis was performed using STATA version 15.1 (STATA Corp., TX).

Fig. 1 Screening, randomization, and analysis

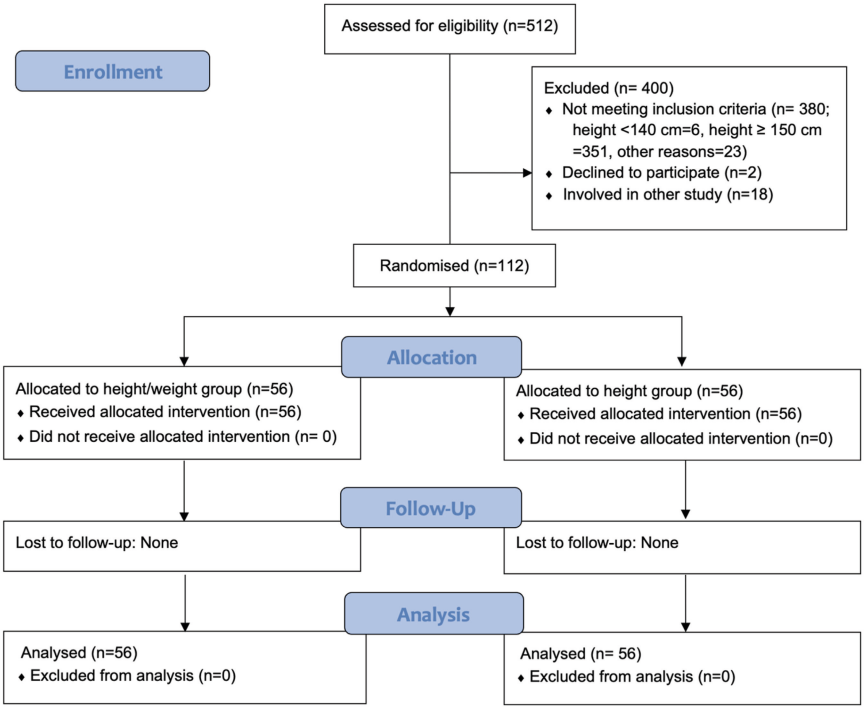


Table 2 Patient demographic and baseline characteristics

Variables	Height/weight-based group (n = 56)	Height-based group (n = 56)	*P*-value
Age (years)	27.2 ± 5.2	26.3 ± 4.6	0.334
Height (cm)	146.3 ± 2.1	145.7 ± 2.3	0.176
Weight (kg)	58.6 ± 7.0	59.4 ± 8.6	0.625
BMI (kg/m^2)	27.4 ± 3.5	27.9 ± 4.0	0.457
Period of gestation (weeks)	39.1 ± 1.3	39.3 ± 1.2	0.432
Anxiety, NRS score*	2 (1-3)	2 (1-4)	0.207
Systolic blood pressure (mmHg)	118.5 ± 9.5	121.4 ± 11.1	0.133
Heart rate (beats/min)	90.4 ± 11.6	89.0 ± 12.4	0.562

Values are in mean ± SD, median (interquartile range)
Abbreviations: NRS, numeric rating scale; BMI, body mass index
**Using a 0-10 cm scale, with zero meaning "no anxiety" and 10 meaning "maximum anxiety"*

RESULTS

A total of 512 patients were assessed for eligibility, of whom 112 were enrolled and randomized into two groups to receive either an adjusted dose of IT bupivacaine based on patient height/weight combined (56 patients) or based on patient height only (56 patients). All patients completed the study (Fig. 1). The baseline characteristics of the patients are presented in Table 2. The mean dose of spinal bupivacaine was 8.33 (0.59) mg in the height/weight-based group and 8.73 (0.28) mg in the height-based group (mean difference − 0.40, *P* < 0.001) (Table 3).

Table 3. Surgical profiles and spinal block characteristics

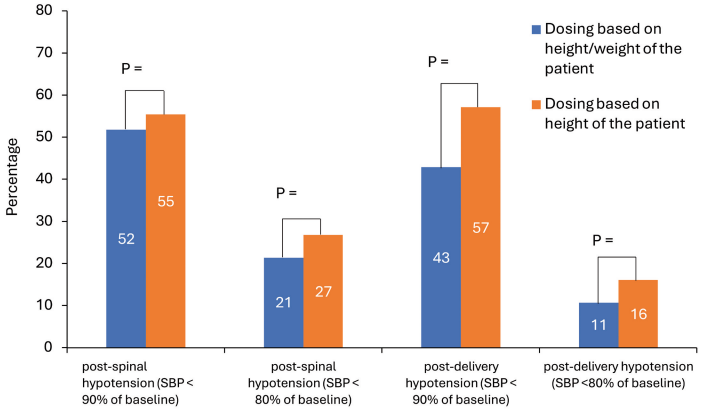
Variables	Height/weight-based group (n = 56)	Height-based group (n = 56)	*P*-value
Spinal bupivacaine dose (mg)	8.33 ± 0.59	8.73 ± 0.28	< 0.001
Induction to skin incision (min)	6.0 ± 2.4	6.6 ± 2.1	0.20
Induction to delivery time (min)	13.8 ± 4.1	14.6 ± 4.3	0.319
Uterine incision to delivery time (s)	60 (30–120)	60 (27.5–120)	0.61
Maximum spread of block height (thoracic dermatome, T)	4 (4–4)	4 (4–4)	0.223
Time to reach block height T6 (min)	3 (3–4)	3 (2–4)	0.399
Motor onset (min)	4 (3–5.5)	4 (3–6)	0.259
Head down tilt needed	3 (5.36)	2 (3.57)	1
2-Segment regression (min)	60 (45–70)	60 (50–70)	0.792
Sensory regression to T10	100 (80–120)	110 (90–125)	0.182
Duration of motor block (min)	130 (120–150)	150 (130–170)	0.059
Total duration of surgery (min)	50 (42.5–60)	45 (40–55)	0.141
Fluid received (ml)	1400 (1300–1500)	1400 (1300–1500)	0.858
Blood loss (ml)	425 (400–550)	500 (400–525)	0.682
Oxytocin needed (Units)	10.9 ± 2.7	11.1 ± 3.3	0.723
Other uterotonic agents used	1 (1.79)	2 (3.57)	1

Values are in mean ± SD, median (interquartile range) and number (percentage)

Post-spinal hypotension (SBP < 90% of baseline) occurred in 29 of the 56 patients (52%) assigned to the height/weight-based group, as compared to 31 of the 56 patients assigned to the height-based group (55%) (absolute difference − 3.5%; 95% confidence interval [CI] − 22 to 14.8; *P* = 0.705). Post-spinal severe hypotension (SBP < 80% of baseline) was observed in 12 of 56 patients (21%) in height/weight-based group and in 15 of 56 patients (27%) in height-based group (absolute difference − 5.3%; 95% CI − 21.1 to 10.4; *P* = 0.508). Post-delivery

hypotension (SBP <90% of baseline) occurred in 24 of the 56 patients (43%) assigned to the height/weight-based group, as compared with 32 of the 56 patients assigned to the height-based group (57%) (absolute difference − 14.2%; 95% CI − 32.6 to 4; *P* = 0.131). Six of 56 patients (11%) in the height/weight-based group and 9 of 56 patients (16%) in the height-based group experienced post-delivery severe hypotension (SBP <80% of baseline), for an absolute difference of − 5.3% (95% CI −17.9 to 7.2; *P* = 0.405) (Fig. 2).

Fig. 2 The percentage of patients who developed hypotension in each trial group.



Height/weight group: no./ total no.	29/ 56	12/56	24/56	6/56
Height group: no./ total no.	31/56	15/56	32/56	9/56

Abbreviation: SBP, systolic blood pressure

Differences in the spinal block characteristics between the two groups are shown in Table 3. More participants in the height/weight-based group than in the height-based group required fentanyl supplementation for intraoperative pain (6 [11%] vs. 0 [0%] participants, *P* = 0.027). Intraoperative nausea occurred in 3 of the 56 patients (5.36%) in the height/weight-based group and in 2 of the 56 patients (3.37%) in the height-based group. Two patients (3.57%) in height/weight-based group and three (5.36%) patients in height-based group developed intraoperative shivering. No patient in either treatment group reported bradycardia (HR < 50/min), vomiting, pruritus or dizziness. None of the patients required rescue ketamine or rescue anti-emetics during the trial. Neonatal Apgar scores at 1 min and 5 min after delivery did not differ significantly between the trial groups. There was no significant between-group difference in the operative quality or patient satisfaction with anesthesia (Table 4). The median duration of pain-free period after spinal anesthesia was 2.4 h (interquartile range 2-3.1) in the height/weight-based group and 2.8 h (interquartile range 2.2-3.55) in the height-based group (*P* = 0.068).

Table 4. Intraoperative maternal hemodynamics, quality of anesthesia, and neonatal outcome

Variables	Height/weight-based group (n = 56)	Height-based group (n = 56)	*P*-value
Pre-delivery lowest SBP (mmHg)	100.9 ± 13.5	103.9 ± 12.1	0.214
Post-delivery lowest SBP (mmHg)	104.8 ± 10.7	105.9 ± 9.7	0.556
Total phenylephrine used (μg)	50 (0-200)	100 (0-200)	0.247
Lowest heart rate (beats/min)	69.7 ± 9.2	71.5 ± 8.4	0.292
Quality of anesthesia			0.067
Excellent	33 (58.93)	34 (60.71)	
Good	15 (26.79)	20 (35.71)	
Fair	2 (3.57)	2 (3.57)	
Poor	6 (10.71)	0 (0)	
Operating condition			0.847
Very good	33 (58.93)	35 (62.50)	
Good	22 (39.29)	21 (37.50)	
Poor	1 (1.79)	0 (0)	
Patient satisfaction with anesthesia, NRS score*	8 (7-9.5)	8 (8-10)	0.542
Neonatal APGAR score (1 min)	7 (7-8)	7 (7-8)	0.697
Neonatal APGAR score (5 min)	9 (8-9)	9 (8-9)	0.604

Values are in mean ± SD, median (interquartile range) and number (percentage)
Abbreviation: NRS, Numeric rating scale
**Using a 0-10 cm scale, with "very dissatisfied" at 0 cm and "very satisfied" at 10 cm*

DISCUSSION

This trial showed that among parturients with short stature, the incidence of post-spinal hypotension and post-delivery hypotension was not significantly different between those who received IT bupivacaine adjusted to height combined with weight, and those who received IT bupivacaine adjusted to height only. We found that patients in the height-based group were less likely than height/weight-based group patients to receive rescue analgesics for intraoperative pain.

Administration of unadjusted spinal local anesthetic doses in short stature parturients is likely to produce hemodynamic instability and a high spinal block. Because unfavorable perinatal outcomes, such as low Apgar scores, are observed in short parturients, any further impairment of uteroplacental perfusion due to hypotension may worsen neonatal outcomes [13]. Therefore, lowering the spinal LA doses in short parturients seems prudent. The LA doses for spinal anesthesia based on patient characteristics are lower than conventional doses,

and these have been shown to produce less maternal hypotension [7-9]. In line with this, we compared two spinal anesthesia dosing regimens based on either height alone or height combined with weight in parturients with heights < 150 cm.

Our study revealed that the intrathecal bupivacaine doses based on height were significantly higher than those based on both height and weight. This difference in dosing is likely due to the linear increase in doses based on height, while doses based on weight are inversely related. This assumption is supported by a population model study that demonstrated a significant correlation between patient height and weight with spinal block characteristics [14]. Despite the differences in the dosing, we did not observe a significant difference in the incidence of hypotension between the two groups. However, Siddiqui and his colleagues found that the incidence of hypotension was significantly higher in the height-based dosing group compared to the height/weight-based dosing group [10]. In their study, the mean height in the height-based group was 155.8 cm, while it was 159.4 cm in the height/weight-based group. Therefore, the significant difference in the patient height may have contributed to hypotension, as previous research has shown a correlation between patient height and hypotension [15, 16]. The other explanation may be due to the different baricities of the bupivacaine used for spinal anesthesia. Unlike the previous study [10] where isobaric bupivacaine was administered, we used a hyperbaric solution. Apart from maternal hypotension, none of the patients in either group developed bradycardia (HR < 50 beats/min). Therefore, in terms of hemodynamic stability, both the regimens of height-based and height/weight-based dosing are appropriate in short parturients.

Lower doses of LA used in single-shot spinal anesthesia may compromise the quality of intraoperative analgesia/anesthesia. A meta-analysis published in 2011 which included 693 participants, reported that the rescue analgesia needed for cesarean section was threefold higher in the low dose group (≤ 8 mg intrathecal hyperbaric bupivacaine) than in the conventional dose group (> 8 mg) [6]. Interestingly, 5% of the 376 patients in the conventional dose group still complained of intraoperative pain. It reflects that we are yet to find the optimal lower doses of intrathecal hyperbaric bupivacaine for CS that produces good intraoperative hemodynamic stability with no compromise in the quality of analgesia. In our study, although both the groups had mean doses of hyperbaric bupivacaine > 8 mg, 11% of the patients in the height/weight-based group required fentanyl supplementation as compared to none in the height-based group. This difference is likely attributed to the higher doses of the bupivacaine administered in the height-based regimen than in the height/weight-based regimen (8.73 mg vs. 8.33 mg). Our observations have indicated that administering a mean difference of 0.40 mg spinal bupivacaine led to a significant decrease in intraoperative pain in the height-based group, while maintaining similar hemodynamics to the height/weight-based group. However, we cannot establish a direct causal link between this association and the observed outcomes. Nevertheless, our findings suggest that for short parturients, using height-based dosing offers the optimal balance between providing effective pain relief during the surgery and reducing the potential for hemodynamic instability.

The ED95 of spinal hyperbaric bupivacaine with an added 10 μg fentanyl for cesarean section in western parturients is 11.2 mg [5]. This dose may be higher for the Asian counterparts because of the differences in body habitus between Western and Asian women. A study in Japanese parturients found that 8 mg of hyperbaric bupivacaine was sufficient to produce adequate analgesia with a lower incidence of hypotension [17]. Likewise, the incidence of hypotension in shorter parturients who received a fixed dose of spinal LA was higher than in the taller group [16]. Whether there is a correlation between height or weight and the spread of bupivacaine in term parturients undergoing cesarean section remains a matter of debate [18, 19]. However, from the patients' safety point of view, it may be necessary to manipulate the neuraxial LA doses in smaller frame pregnant women.

LIMITATIONS

This study has several limitations. First, the trial was conducted in a Nepalese population, thus limiting its generalizability. Second, we had to exclude patients with heights less than 140 cm because the bupivacaine doses for this group of patients were not available in the chart by Harten and colleagues. As a result, we could only study a narrow range of patients with heights between 149 and 140 cm. Third, due to variation in maternal ethnographic origin, there is no uniformity in the cut-off points of heights for identifying short stature women. We defined parturients with heights less than 150 cm as short stature because adverse obstetric outcomes are reported in Nepalese parturients with heights < 150 cm as compared to those with heights > 150 cm [20]. At last, although recommended in most guidelines, we did not use the prophylactic phenylephrine infusion to counter post-spinal hypotension. However, unlike most studies that used post-spinal hypotension definition as SBP < 80% of baseline, we defined our primary outcome, as a SBP < 90% of baseline.

CONCLUSION

Our study found that in short-statured parturients undergoing cesarean section, the effect of a height-based regimen for spinal anesthesia on post-spinal hypotension did not differ from a height/weight-based regimen. However, the height/weight-based group required intraoperative rescue analgesia more frequently. Therefore, administering spinal anesthesia based on the height in a short-statured women can offer a favorable balance between ensuring pain-free anesthesia during a cesarean section while minimizing the possibility of hemodynamic instability.

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Chapter 7

Postdural puncture headache: Revisited

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ABSTRACT

Postdural puncture headache (PDPH) may develop after an unintended (accidental) dural puncture, after deliberate dural puncture for spinal anaesthesia or during diagnostic dural punctures performed by other medical specialties.

PDPH may sometimes be predictable (patient characteristics, inexperienced operator or comorbidities), is almost never immediately evident during the procedure, and sometimes presents late, after discharge. Specifically, PDPH severely restricts activities of daily living, patients may be bedridden for several days and mothers may have difficulty in breastfeeding.

Although an epidural blood patch (EBP) remains the management technique with greatest immediate success, most headaches resolve over time but may cause mild-severe disability. Failure of EBP after the first attempt is not uncommon, and major complications may occur but are rare.

In the current review of the literature, we discuss the pathophysiology, diagnosis, prevention and management of PDPH following accidental or intended dural puncture, and present possible therapeutic options for the future.

INTRODUCTION

Postdural puncture headache (PDPH) has puzzled clinicians ever since its first case description by August Bier in 1898 because underlying mechanisms are still not completely understood. Since it is iatrogenic in nature it is important to understand the pathophysiology of PDPH to offer better treatment options. Many prophylactic and therapeutic options were explored, however none of these could be recommended for routine use until the epidural blood patch (EBP) was first used by Gormley in the 1960s, which is today considered by many to be the best choice, specifically in patients with severe PDPH.[1]

PDPH after neuraxial anaesthesia or analgesia procedures continues to affect many obstetric and non-obstetric patients, including about 0.5-1% of mothers receiving epidural analgesia during labour. This is primarily due to the loss of CSF following a meningeal puncture, either intentional or accidental. Smaller diameter spinal needles and better design have reduced the incidence and severity of PDPH after spinal anaesthesia. However, PDPH after accidental dural puncture (ADP) in obstetrics or after diagnostic lumbar puncture continues to be a problem, while novel neuraxial interventional procedures in oncology, pain medicine and neurology contribute to an increased incidence of PDPH. The term PDPH may be considered a misnomer, as not just the dura mater, but also the arachnoid membrane containing the CSF must be breached.

Causes of PDPH

Postdural puncture headache can occur after various neuraxial procedures which are listed in Box 1. Today, the commonest cause of PDPH is an accidental puncture of the meninges during insertion of the epidural needle for labour analgesia. ADP may be evident immediately due to the return of cerebrospinal fluid (CSF) in the epidural needle (>50% of patients) or later when classical symptoms of PDPH manifest without observed CSF. PDPH may also result from a deliberate neurologic diagnostic or therapeutic meningeal puncture or following spinal anaesthesia. Smaller-sized spinal needles with improved atraumatic design have reduced the incidence of PDPH after spinal anaesthesia, but not everywhere, as atraumatic needles are often unavailable or unaffordable. Perioperative lumbar spinal drains to prevent ischemia of the spinal cord in vascular surgery, diagnostic myelogram, CSF drainage in idiopathic intracranial hypertension, intrathecal drug provision and epidural/intrathecal implantation of neuromodulation devices can all cause PDPH.[2-5] Finally, a small group of patients may develop spontaneous intracranial hypotension (SIH) due to leakage of CSF in the cervical-thoracic or lumbar region, which also causes headaches resembling PDPH.[6]

Box 1. Causes of PDPH

Accidental
- Following epidural anaesthesia or analgesia (obstetric or non-obstetric)
- Following epidural lead implantation in neuromodulation

Interventional
- Following spinal anaesthesia for surgery
- Following spinal analgesia in CSE

Diagnostic
- Diagnostic lumbar puncture in neurological or infectious diseases

Therapeutic
- Injection of cytotoxic drugs or antibiotics intrathecally
- Lumbar CSF drainage for vascular surgery
- Intrathecal leads implanted for neuromodulation
- Intermittent CSF drainage in Idiopathic Intracranial Hypertension

Spontaneous
- Spontaneous Intracranial Hypotension

Incidence of PDPH

Depending on the cause of PDPH, the incidence varies considerably. After spinal anaesthesia it occurs between 0.3% and 40%, depending on several factors such as age, gender, needle size and needle type. Sharp traumatic spinal needles result in PDPH significantly more often, regardless of needle size.[7,8] In wealthy countries, the incidence of PDPH after spinal anaesthesia has dropped to as low as 0.16% in non-obstetric and 1.2-3% in obstetric patients due to the use of non-traumatic pencil-point needles.[9,10] The current incidence of ADP following epidural analgesia in labour is <1% and approximately 50-80% of these patients with an ADP develop PDPH.[11] After a diagnostic lumbar puncture, PDPH rates of up to 50% are described, which have decreased to <6% following the introduction of atraumatic needles.[12,13] The use of neuroprotective spinal drains in thoracoabdominal aortic repair causes PDPH in approximately 18% of patients, while the incidence of PDPH after epidural lead placement for spinal cord stimulation was 0.8% per lead insertion.[2,3] In paediatric anaesthesia, the incidence of PDPH has increased as spinal anaesthesia has become more popular, even in very young children.[14]

PATHOPHYSIOLOGY OF PDPH

The one factor presumed to be essential for the development of PDPH is loss of CSF. However, this does not always result in PDPH, nor is PDPH always preceded by identified CSF loss, as in many instances PDPH can occur after uneventful epidural labour analgesia without any evidence of ADP. Two underlying mechanisms for PDPH are thought to be involved: traction/compression of pain-sensitive intracranial structures and intracranial vasodilation. CSF loss from the spinal intrathecal space to the epidural compartment increases CSF flow from the intracranial to the extracranial space. This reduces intracranial CSF volume which affects the

cushioning of the intracranial cerebral components and causes traction/pressure on pain-sensitive intracranial structures leading to headache and other associated symptoms. The other potential source of headache is vasodilation, which is either compensatory, to retain balance within the intracranial space in accordance with the Monro-Kellie doctrine, or reflex vasodilation resulting from traction on intracranial vessels.[15,16] In the early 20th century, many experimental studies showed that extraction of CSF led immediately to headache symptoms, which disappeared once CSF was returned to the intrathecal space. However, this alone cannot explain the mechanism as some patients suffer from severe PDPH after uneventful spinal anaesthesia with small gauge atraumatic needles and minimal CSF loss. Furthermore, patients having continuous CSF loss via a subarachnoid-cutaneous fistula or patients with radiological signs of intracranial hypotension do not always present with PDPH.[17,18] Patients with spontaneous intracranial hypotension (SIH) undergoing repeated lumbar punctures show varying lumbar CSF opening pressures unrelated to the presence/absence of headache symptoms, which suggests that a decreased CSF volume instead of CSF pressure could be considered pathognomonic.[6,19,20] To increase knowledge of the underlying pathophysiology and challenge presumed concepts, one has to better understand the anatomy and physiology of mechanisms involved in PDPH.

Anatomy

Although dural puncture suggests that the dura mater has to be penetrated to cause CSF leakage, it is actually the middle layer, the arachnoid mater containing the CSF that has to be punctured to cause loss of CSF. Therefore, a more appropriate name would be post-meningeal puncture headache or post-arachnoid puncture headache.[11,21] The spinal dura mater begins at the foramen magnum and ends caudally in the coccygeal membrane, its thickness varies between individuals and decreases over a lifetime. The dura is considered a predominantly supportive membrane, but it is also a complex vascularized and innervated structure, with poorly understood contributions to the homeostasis of the CNS.[22] It is the arachnoid mater which contains CSF in the intrathecal space. Once breached CSF loss occurs, the magnitude depending on the size of the hole and the extent of damage and subsequent repair of the arachnoid lesion.[23] The arachnoid consists of two layers, the inner trabecular layer providing a mesh-like spider web and the outer layer which consists of tightly connected arachnoid cells and collagen fibres lining the inside of the dura mater.[23]

CSF

CSF, consisting of 99% water, provides cushioning protection for vulnerable brain components and also plays an important role in brain parenchymal homeostasis.[24] It facilitates metabolite/waste exchange throughout the CNS, which is essential for optimal neuronal functioning. CSF volume is higher than previously thought, approximately 250 ml, its production is not limited to the choroid plexus and resorption occurs even away from the arachnoid granulations.[25] Microscopic water/solute/waste exchange also occurs in the

perivascular spaces surrounding subarachnoid blood vessels, and instead of a unidirectional bulk flow in the spinal subarachnoid space, there is a significant multidirectional oscillatory CSF flow resulting from respiratory and hemodynamic pressure variations. Additionally, gravity and body position contribute to craniospinal motion.[24,26-29]

SYMPTOMS AND SIGNS

Irrespective of the cause of PDPH, symptoms are similar although intensity and duration may differ. PDPH presents as a dull, throbbing, bilateral headache which appears within 5 days of a lumbar/spinal procedure, often frontal and/or occipital located and accompanied by neck pain, audiovisual symptoms and nausea (See box 2).

Box 2. Common symptoms and signs of PDPH

Headache (frontal, occipital, neck, temporal) that is mostly, but not invariably, postural in character
Auditory symptoms (tinnitus, hearing loss)
Visual symptoms (diplopia)
Dizziness
Nausea and/or vomiting
Symptoms and signs resulting from involvement of cranial nerves

Symptoms may increase during sneezing or coughing, are worse in the upright position and usually, but not invariably, improve in the supine position, although atypical presentations occur, both in SIH and after meningeal puncture.[30,31] The intensity of headache can be very severe (NRS 7-10) and is often disabling, especially after meningeal puncture with a large traumatic needle. In a large observational study on PDPH after ADP in obstetrics the most common symptoms, other than headache and neck pain were dizziness (24%), nausea and/or vomiting (22%), auditory symptoms (18%) and visual symptoms (13%).[32] Nausea, vomiting, vertigo and dizziness can be related to vestibulocochlear disturbances, traction on the vagus nerve resulting in stimulation of the chemoreceptor trigger zone, or caused by pain and discomfort.[33] Changes in hearing acuity and tinnitus appear within days and sometimes have a postural component. These auditory symptoms are the result of transmission of abnormal CSF pressure to perilymph in the cochlea, causing an imbalance between peri- and endolymph which affects the relationship between hair cells and basement membrane.[33,34] Diplopia results from stretching of the abducens nerve over the bony structures of the skull. The ensuing neuropraxia causes symptoms that appear after a few days but sometimes may persist after the headache has resolved.[33] Unilateral facial or tongue numbness, related to trigeminal and facial nerve injury or palsy may occur following PDPH.[33] Physical examination usually does not reveal further information except that the patient prefers lying down as this reduces the severity of symptoms. In case of cranial nerve compromise, symptoms are seldom permanent but resolve, though much slower than headache symptoms, over a period of weeks/months.[33]

Box 3. Diagnostic criteria for PDPH (ICHD-3)

A. Headache fulfilling criteria for 7.2 Headache attributed to low CSF pressure*
B. Dural puncture has been performed
C. Headache develops within 5 days of dural puncture
D. Not better accounted for by another ICHD-3diagnosis

It is usually accompanied by neck stiffness and/or subjective hearing symptoms. It remits spontaneously within 2 weeks, or after sealing the leak with an autologous epidural blood patch
**Modified in 2018 to add that the headache is "usually but not invariably orthostatic"*

Diagnosis

The diagnosis of PDPH, irrespective of the nature of the meningeal puncture is clinical and based on the diagnostic criteria of the ICHD-III listed in Box 3.[35] The ICHD-3 states PDPH should be fulfilling the criteria of headaches attributed to low cerebrospinal fluid pressure i.e. demonstration of either low CSF pressure (<60 mmHg) or evidence of CSF leakage on imaging. However, in clinical practice, this criterion is seldom fulfilled since CSF pressure is not measured and routine radiological imaging is not performed. Instead, the clinician relies upon the presence of headache symptoms appearing within 5 days of a suspected or intended meningeal puncture, not better accounted for by another diagnosis for confirming PDPH, especially if neck stiffness or hearing symptoms are present. The most important diagnostic feature of PDPH, worsening of symptoms within 15 min of sitting/standing and improving within 15 min after lying down, has recently been changed to 'often but not invariably' since some patients, despite a confirmed PDPH, have no or minimal orthostatic component.[30,32] This makes a definite diagnosis of PDPH challenging, especially after an intended meningeal puncture or during epidural insertion where PDPH can occur without evidence of a definite ADP (CSF in epidural needle), as in up to 40% of patients where other causes of postpartum headache are present.[36,37] (see differential diagnosis box 4).

Box 4. Differential diagnosis of postpartum headaches

Common causes	Uncommon causes
Tension headache	Subarachnoid bleeding
Lack of sleep	Cortical/sagittal vein thrombosis
Dehydration	Pre-eclampsia/Eclampsia
Migraine	Reversible cerebral vasoconstriction syndrome
Caffeine	Withdrawal other drugs/substances

Radiological imaging may be useful in ruling out other pathology or corroborating an unclear presentation. MRI findings typical of PDPH, although not always present, include dural venous engorgement that may result in pressure-driven extravasation of fluid, seen as abnormal pachymeningeal enhancement of the innermost dural layers. Other characteristic features may be decreased size of subarachnoid cisterns and cerebral ventricles, downward

displacement of the brain ('sagging') and pituitary gland enlargement.[38] Once the diagnosis of PDPH is confirmed, a changing presentation such as increased severity, disappearance of the initial positional component, lateralization of symptoms, new onset of nausea, vomiting, neurologic focal symptoms or sedation and coma require immediate additional diagnostic studies and multidisciplinary management.

RISK FACTORS FOR PDPH

The incidence of PDPH decreases with age, which may be due to changes in elasticity of the dura mater, a reduced response of cerebral vessels to loss of CSF or smaller epidural space.[39,40] Regardless of pregnancy, women are at higher risk of PDPH, probably due to the increased amount of circulating oestrogens that may affect the tone of the cerebral vessels and their response to a decrease in CSF pressure; differences in nociception processing between men and women might contribute to this higher risk as well.[39,41] During pregnancy, several factors contribute to an increased risk, such as further elevation of oestrogen levels, increase in intra-abdominal pressure, increased CSF pressure during second-stage pushing and dehydration secondary to NPO status, blood loss or post-partum diuresis.[42] A history of chronic headaches or PDPH results in a higher risk of developing PDPH. However, a history of migraine is not related to an increased risk of PDPH.[13,16] Obesity is thought to be protective in the development of PDPH since increased intra-abdominal pressure increases epidural pressure, which limits CSF loss after meningeal puncture. Data on PDPH after ADP in the obstetric population are conflicting, but following lumbar puncture, a low BMI is associated with an increased incidence of PDPH.[12,13,43,44]

Prevention

Patient-related factors for PDPH include age (younger), gender (female), pregnancy and a previous history of headaches. The main modifiable factor that has been demonstrated to reduce the incidence of PDPH after spinal anaesthesia is the spinal needle design.[9,45] Atraumatic pencil point needles result less often in PDPH. They cause blunt irregular tearing and more damage to the dura/arachnoid membrane, in contrast to the clean crescent-shaped cut resulting from a puncture with a sharp traumatic needle.[46] Why this extended damage leads to a reduced incidence and severity of PDPH has not been determined, does it contribute to a quicker healing process? While needle size seems quite irrelevant for pencil point needles, when traumatic sharp needles are used, smaller needles result in less PDPH.[9,45] Spinal needle insertion parallel to the spinal axis has been associated with a reduced risk for PDPH if traumatic needles are used, although this cannot be explained by the previously incorrectly assumed longitudinal orientation of dural fibres.[47,48] Paramedian spinal approaches to reduce PDPH have shown conflicting results, but greater experience of the provider might reduce multiple attempts or ADP.[12,49-51] Bed rest after lumbar puncture does not reduce the incidence or duration of PDPH.[52] A recent practical guideline recommends using

atraumatic needles for neurologic diagnostic and therapeutic lumbar punctures, which show equal efficacy to conventional needles but reduce the incidence of PDPH by >50%.[53,54] Can PDPH be prevented once an ADP occurs? Following an observed ADP many preventive measures have been proposed, ranging from re-siting the epidural at another level for labour analgesia (sometimes followed by injecting autologous blood (prophylactic EBP) or epidural morphine through the catheter before removal), to inserting the epidural catheter intrathecally and providing spinal analgesia.[21,55-57] Assisted vaginal deliveries and elective caesarean sections have been associated with a reduced incidence and severity of PDPH.[42,44] The use of a 'prophylactic blood patch' in patients with ADP has been attempted but is no longer recommended.[58,59] Injection of epidural morphine in order to prevent PDPH after ADP has been shown to indeed reduce the incidence of PDPH and the need for an EBP.[57]

The insertion of an intrathecal catheter (ITC) through the epidural needle that caused the ADP is considered a strategy to reduce the incidence and severity of a subsequent PDPH.[56,60] The are several advantages of an ITC: the need to perform a new epidural with the risk of a new ADP is avoided, patients can get immediate relief of labour pain using the spinal catheter and one could use it for spinal anaesthesia if needed for a caesarean section. However, there are attendant risks, since the catheter may be accidently used as an 'epidural' catheter, and there is also a potential risk of infection. ITC prevents further CSF loss, and although inert, allows time for an inflammatory response, which facilitates rapid closure of the breach once the catheter is removed. Whether an ITC reduces the risk of a subsequent EBP has been explored and some studies seem to support this belief, but the evidence remains inconclusive.[56,60,61] For a more comprehensive review of ITC, readers are referred to an excellent review published recently.[62] Randomized studies are urgently needed in the literature to determine the use of this technique as a proactive management strategy when ADP is clearly evident during epidural needle insertion. The most important step to reduce the incidence of PDPH is to prevent ADP. Supervised training in obstetric anaesthesia followed by frequent performance to increase the 'volume' of epidurals inserted are prerequisites for maintaining a low frequency of ADP in training institutions. The use of ultrasound techniques should be encouraged so as to identify the midline, the level of the lumbar puncture and the depth of the epidural space.[63] This may be specifically useful in patients with vertebral column pathology, obese patients and those in whom there was previous difficulty in establishing an epidural block. Finally, experienced anaesthesiologists should either perform or supervise labour epidurals in complex patients to prevent the occurrence of an ADP. Using smaller 18 G Tuohy needles instead of 16 G, air instead of saline for detecting loss of resistance, inserting the epidural at L2-L3 compared to L3-L4, and inserting an ITC after ADP have all been associated with a reduced risk of subsequent EBP to treat PDPH in a recent prospective observational study.[32]

COMPLICATIONS

The self-limiting character of PDPH, either spontaneously or after an EBP, should be questioned: chronic symptoms have been reported as early as 60 years ago when 6%-13% of patients had persistent symptoms after spinal anaesthesia.[35,64] Recent studies describe chronic headache and backache symptoms with widely varying incidences, depending on the cause of PDPH, the definition of headache used and the duration of symptoms. Headaches lasting longer than 6 weeks have been reported in 28-58.4% of obstetric patients after ADP, with almost similar incidences at 18 months.[65-68] In a large database study, PDPH was associated with an increased adjusted OR of 7.7 for a diagnosis or readmission for chronic headache or migraine, and OR of 4.4 for chronic back pain.[69] A recent systematic review and meta-analysis found an increased risk of headache, backache and neckache at 12 months after ADP in obstetric patients, with the authors unable to demonstrate a significant reduction after EBP.[70,33] 2 retrospective studies identified an association between PDPH and postpartum depression, which also needs further investigation.[69,71] These long-term consequences of PDPH, occurring at higher rates in obstetric patients than previously thought, can no longer be ignored, as they affect maternal well-being and may result in chronic ailment with potential socio-economic consequences. Optimizing neuraxial techniques, material and efforts to prevent ADP and PDPH are mandatory to avoid chronic sequela. Furthermore, patients should be informed during the consent process of the potential complications of various neuraxial procedures. Subdural haematoma (SDH) is the most feared complication of PDPH. Recent database studies using hospital admission records provide staggering insights into the relationship between PDPH and subdural haematoma. Moore reported an OR of 199 after neuraxial anaesthesia in childbirth, while Guglielminotti described an OR of 19 for the composite outcome of cerebral venous thrombosis/subdural haematoma in PDPH patients compared to women without PDPH.[69,72] Both publications reported comparable incidences of SDH after elective caesarean or vaginal deliveries. The diagnosis of SDH may be difficult as symptoms may be attributed to PDPH and do not change substantially before subdural haematoma is detected.[73-75] SDH is not always related to severity of PDPH. A recent review suggested that most subdural haematomas reported in the literature occurred after intentional dural puncture, with <50% of cases originating from the obstetric population.[73,74] The underlying mechanism is thought to be the rupture of thin-walled subdural veins between the dura and arachnoid membrane after CSF loss and subsequent brain sagging. Other factors such as coagulation disorders, intracranial vascular abnormalities and second-stage pushing might contribute to its occurrence in a minority of obstetric patients.[75] Early recognition of SDH is essential in order to initiate treatment, but diagnosis is not always easy. Sensory disturbances, motor deficit and reduced level of consciousness may be present in some cases, but Cuypers identified focal neurologic symptoms in 69% of cases, with persistent headache losing its postural component as a common symptom.[73-75] Therefore, undetected cases of SDH might accompany PDPH.

CONSERVATIVE (NON-INTERVENTIONAL) MANAGEMENT OF PDPH

When the diagnosis of PDPH is confirmed, irrespective of aetiology, most anaesthesiologists prefer conservative management initially, unless the headache is very severe and disabling. In most patients, symptoms subside gradually over time and an EBP was shown to be more successful if applied after 24-48 h.[76] However, conservative treatment without reduction of symptoms may eventually lead to intracranial bleeding due to stretching of the meninges from a 'sagging' brain. Patients need close surveillance to identify either worsening symptoms or the appearance of new symptoms. These patients require either an early EBP or further diagnostic procedures to exclude other intracranial pathology. Common strategies used for conservative management are shown in Box 5, the evidence behind these strategies is discussed below.

Box 5. Conservative management strategies

Hydration and fluid therapy (orally/intravenously)
Bed rest/delayed mobilisation
Analgesics
Caffeine
Others
(good evidence for most of the above strategies is either limited or lacking)

Hydration

It was believed by some that dehydration may be a factor influencing the incidence of PDPH since it is high in pregnant women after delivery when fluid intake is low and fluid losses high. Therefore, it became common practice to rehydrate patients prior to spinal anaesthesia. Although volume preloading reduced the incidence and magnitude of spinal anaesthetic-induced sympathetic blockade, evidence is inconclusive regarding the incidence of PDPH.[52,77] Today it is recommended that normal hydration of the patient should be maintained. Extra hydration does not alleviate the headache but dehydration makes symptoms worse.

Bed rest or delayed mobilization

Placing a patient horizontally for a period of time after a dural puncture does not affect the incidence or duration of PDPH but delays the onset of the PDPH until mobilization.[52,78] Due to the severe headache in the upright position, patients nevertheless prefer bed rest initially to avoid the discomfort associated with an upright position. A lateral horizontal position produces less tension on the dural injury than a supine position and may result in less leakage of CSF. In one study in patients having spinal anaesthesia for surgery, the authors found a lower incidence of PDPH in the group that was maintained in the prone position postoperatively compared to the supine position.[79] Today, early mobilization is

recommended to the extent that the patient can be out of bed. This has the additional benefit of reducing the risk of deep vein thrombosis when immobilized.

Analgesics

Irrespective of the cause of the headache (PDPH), pharmacological management is commonly initiated, specifically during the 'observation period' of 24-48 h before a definite decision is made as to how to proceed. Analgesics commonly used by oral or intravenous routes provide varying degrees of pain relief and are a first line for management. No specific analgetic is better than another, physicians tend to use mild analgesics such as paracetamol or NSAIDs for the mild headache going over to stronger (opioid-based) analgesics for more severe cases. Box 6 shows a summary of the common analgesics used today.

Box 6. Analgesics used to relieve PDPH

Paracetamol
Non-steroidal anti-inflammatory agents (NSAIDs)
Opioid-analgesics (oral, intravenous, epidural, intrathecal): Morphine
Other drugs: Steroids, ondansetron, dexmedetomidine, magnesium, ketamine
Regional blocks: Sphenopalatine ganglion block, greater occipital nerve block

Many drugs have been considered for treatment, with gabapentin, amino/theophylline and hydrocortisone showing some decrease in pain severity scores, while data on other drugs such as sumatriptan and ACTH are more inconclusive.[80] There are many publications in the literature on the use of caffeine to relieve the symptoms of PDPH with mixed results. The evidence today seems to point towards a lack of efficacy, possibly a placebo effect. Its therapeutic benefits therefore seem questionable and caffeine in any form cannot be recommended as a routine management technique for PDPH.[80,81] Several uncommon prophylactic and therapeutic strategies have been recently tried to reduce the incidence and severity of PDPH after various neuraxial procedures, such as ketamine, magnesium, dexmedetomidine, neostigmine, ondansetron etc., but the evidence is limited and recommendations cannot be given yet. A recent observational case series described patients with severe PDPH who were given high-flow oxygen through a non-rebreathing mask and experienced immediate relief without return of symptoms, can this be confirmed in prospective randomised studies?[82] Similarly, sphenopalatine ganglion blocks (SPGB) and greater occipital nerve blocks have been used to resolve PDPH symptoms, sometimes successfully, but the evidence remains unconfirmed until more studies are performed.[83-85]

INTERVENTIONAL MANAGEMENT

Epidural blood patch (EBP)

The use of autologous blood injected in the epidural space as treatment for PDPH was first considered around 1960 when James B. Gormley, a surgeon, observed that after a bloody spinal tap (for spinal anaesthesia) patients rarely developed any PDPH. Subsequently he successfully introduced the intrathecal injection of saline followed by epidural injection of 2-3 ml of autologous blood during needle withdrawal.[1] Continuing work of DiGiovanni, Crawford, Paech and others eventually led to the current use of 20-30 ml blood, as the epidural mass effect is considered to be the most important factor driving the success of EBPs.[76] It took a while longer before EBP was introduced to treat PDPH resulting from other procedures and SIH, with varying success.[86-88]

Why are EBPs successful?

The precise underlying working mechanism is thought to be two-folded. First, the instant relief of symptoms after application of the EBP is considered to be the result of the epidural injection of a certain volume of blood and its immediate epidural mass effect. Second, the injected blood will clot adjacent to the dural damage and prevent further leakage of CSF while the dural/arachnoid membrane repairs. The epidural mass effect has been demonstrated in SIH patients, with subarachnoid spinal and intracranial pressures and its surrogate, the optic nerve sheath diameter (ONSD) measured by ultrasound, responding immediately with parallel relief of symptoms.[89,90] This immediate increase in intracranial CSF volume and pressure may reduce traction on pain-sensitive structures and vasodilation. As compliance of the epidural space is highly variable between patients, the volume needed to achieve an initial mass effect is difficult to predict, which has led to the practice of injecting blood until the patient complains of symptoms such as back ache or radiating pain.[91,92] The injected epidural blood spreads circumferentially with a preference for cephalad distribution, the resulting dural sac compression still visible on MRI 3 h after injection.[93,94] The second effect of an EBP is the formation of an epidural blood clot adjacent to the meningeal damage. This mature clot tissue is thought to contribute to the repair of the lesion in the meningeal membranes, and appears to be present locally till at least 18 h after application of the EBP.[94] Permanent repair of the meningeal opening is dependable on the local inflammatory reaction, with more damaged tissue produced by non-cutting needles resulting in faster closure of the traumatic lesion.[46] Other unknown factors might be involved, as the following questions remain unanswered. Why is it that EBPs at lumbar levels are also successful in treating PDPH in SIH resulting from dural tears at cervical or thoracic levels?[95,96] Why do EBPs in obstetric patients with PDPH provide complete initial relief in only one in three patients, and why are other factors, especially the timing of an EBP, related to its success or failure?[32,97]

Indications for an EBP

Conservative management without an EBP may be a good alternative in many patients since the natural course is generally one of a gradual reduction of symptoms. Without active intervention in obstetric patients experiencing PDPH, >80% have mild or no headache one week after ADP.[32] However, with serious symptoms which do not subside or increase in severity over time, an early EBP might be indicated, even if it implies a second EBP, as PDPH is related to severe disability and suffering, temporary damage to cranial nerves and subdural haematoma. Delayed application of an EBP has been associated with an increased incidence of subdural haematoma in the obstetric population.[72] Other indications for an EBP are PDPHs after other neuraxial procedures and patients experiencing PDPH-like headaches resulting from SIH.

Contraindications for EBP

The same contraindications apply as for epidural needle placement, such as local skeletal and/or neurological abnormalities, myelomeningocele, tethered cord, patient refusal, the presence of coagulopathy or the use of coagulants and signs of infection, either systemic or local at the proposed injection site and lastly the risk of CNS herniation in patients with an intracranial space-occupying lesion.[98]

Why do EBPs fail, and can this be avoided?

There is no consensus in the literature regarding the definition of a failed EBP. While some studies consider persistent headache or recurring headache, whatever its intensity, as a failed EBP, others define it as the need for a second EBP.[76,91] EBPs have also been classified as partial or complete failures or described as initial success with permanent relief or initial success and subsequent failure.[99-101] Depending on the definition, a failed EBP may occur in 7-66% of patients.[76,100,102] In a recent large observational study, the authors classified headaches after EBP as mild (NRS <3), moderate (3-6) and severe (>6).[101] Using this definition, moderate-severe headache post-EBP was seen in >30% of patients and approximately 20% received a second EBP. Considering that application of an EBP is an invasive procedure associated with complications, failure rates are quite high and therefore it is important to understand the reasons for EBP failure.

Factors related with the success and failure of an EBP

Timing

There is no consensus regarding the timing for application of an EBP. When only considering the risk of failure, waiting 24-48 h seems appropriate, as early provision is associated with increased failure.[76,101] However, in patients with severe symptoms, evidence of 'sagging' on CT examination or signs of cranial nerve involvement (ocular, auditory, abducens nerves), it may be wise to proceed earlier with an EBP. Prophylactic EBP's have been used in the past in obstetric patients after ADP, using a second epidural catheter inserted after the first EDA attempt resulted in an ADP. Sealing the dural damage after delivery with autologous blood

before symptoms arose, was considered to prevent further CSF loss and the occurrence of PDPH. Until now evidence is not supporting the use of prophylactic EBP, as it does not decrease the incidence of PDPH significantly, with its failure associated with potential dilution of the injected blood by either local anaesthetic or CSF, which both may affect clot formation and clot stability.[58,103-105] Contrary to the USA, where an early EBP after ADP in patients with severe PDPH is not uncommon even though the risk for a second EBP is high, in Europe the tendency is to start with conservative measures first and wait to see if symptoms decrease before application of an EBP.[55,101,106] Late EBP provision, apart from causing prolonged suffering and pain, might be associated with an increased risk of cranial nerve compromise and subdural haematoma resulting from continuous low CSF pressure.[72] Moore demonstrated that women with PDPH in childbirth who received an EBP during a hospital re-admission (late), had an adjusted absolute risk increase of 130 per 100.000 deliveries of having a subdural haematoma, although the precise timing was not specified in this study.[72]

Location

The current recommendation is to administer the EBP below the level of the original dural puncture to enhance success, but Gupta et al. recently failed to demonstrate an association between EBP success and the level of insertion of the EBP in relation to the level of the initial dural puncture.[93,94,101] Only the level of the initial ADP was relevant to the success/failure of the EBP; the higher the initial ADP, the greater the risk of failure of a subsequent EBP.[101] In SIH it was thought that an EBP targeted near the meningeal lesion had a higher success rate, but a recent study demonstrated similar efficacy when targeted and non-targeted levels for an EBP were used. A distant lumbar EBP might be preferable and effective in patients with challenging cervical or thoracic lesions.[96,99,107]

Volume

The role of volume in the working mechanism of EBPs is incompletely understood. Pratt et al. have demonstrated that, although there is a curvilinear relationship between the volume of blood injected and the epidural pressure, there is a wide variety of epidural pressures generated, unrelated to the success of the EBP.[92] The current advice is to use up to 20 ml unless symptoms occur earlier, based on one of the few RCTs on EBP volume in women experiencing PDPH after ADP, which concluded that using 30 ml provided no additional benefits while causing more often pain during injection.[76,97] In patients with SIH, higher volume was the only factor significantly related to a higher success rate of the EBP.[96,99] There is limited data regarding EBP volume in children. While generally 0.3 ml/kg has been suggested, Kokki et al. reported that 0.2 ml/kg resulted in permanent relief in 85% of patients who experienced PDPH either after lumbar puncture or spinal anaesthesia.[108] Whatever volume is chosen, one should stop injecting once the patient complains of back pain, neck pain or radicular symptoms.

Does EBP reverse the accompanying symptoms of PDPH?

Most cranial nerve symptoms accompanying PDPH are relieved within weeks/months after an EBP, apart from the auditory symptoms, which resolve rapidly.[33,34] But several years after having received an EBP for PDPH in obstetrics, a minor hearing loss can still be found with pure tone audiometry (<5 dB) at low frequencies.[34] Some cranial nerve disturbances actually appear only after application of the EBP, which is thought to result from compromised vasa nervosum surrounding cranial nerves due to sudden increases in intracranial pressure after EBP.[33]

How to patch?

Imaging is not necessarily recommended when classical symptoms of PDPH are present in relation to a recent neuraxial procedure unless a sudden change in presentation demands exclusion of other causes. The same precautions and preparations as for an epidural injection should be applied, and standard monitoring and intravenous access are advised as some patients will respond with bradycardia to injection of fluids in the epidural space.[97]

Once the epidural needle is advanced to the epidural space, autologous blood (up to 20 ml) should be drawn through a second intravenous needle under strict aseptic conditions, which can then be injected through the epidural needle until patients complain of backache, discomfort or radiating pain.[76,97] Ultrasound might improve correct identification of the epidural space, while fluoroscopic guided EBP has shown to result in a higher success rate and the use of a lower volume.[107,109,110] Duration of immobilization appears to be unrelated to EBP success/failure; only one small study associated longer immobilization (2 h) with success of EBP, while Gupta rather found a tendency towards more complete failures in patients mobilized later (>4 h).[97,101,111] Patients should be advised to avoid heavy exercise, lifting and bending after the procedure, as this might interfere with closure of the dural injury.

Are there any complications of an EBP?

An EBP, although an invasive technique, is considered a safe procedure, but complications can occur. Risks are comparable to all neuraxial procedures such as the risk of another accidental dural puncture, nerve root irritation by the needle and infection. Spreading of the blood along the nerve roots can cause temporary radicular irritation, and back pain is often described, resulting from subcutaneous, muscular and/or tissue irritation due to the presence of blood.[112,113] Although seldom occurring, more severe complications such as spinal subdural or intrathecal haematoma have been reported.[114] After an EBP in SIH patients Ferrante et al. visualized subarachnoid blood in 8.5% of patients, unaccompanied by arachnoiditis or clinical symptoms.[115] Both cerebral venous thrombosis and subdural intracranial haematoma have been described during PDPH, with an unknown association with EBPs.[69,72,116] Arachnoiditis, transient bilateral paraplegia and retinal haemorrhage have also been reported after EBP treatment.[117-120] Recent studies have shown a relationship between development of chronic symptoms such as backache or headache and PDPH, without evidence of the EBP contributing to a significant reduction, with one study

actually demonstrating an increased incidence in chronic low back pain occurring after EBP.[70,71,113,121]

How to proceed after a failed EBP?

The incidence of failure of an EBP varies, and a patient might experience only partial relief or a return of symptoms. A second EBP might be considered after excluding other causes of headache, but only if symptoms and signs are similar and not changing or fluctuating. In case of any doubt, multidisciplinary consultation and additional imaging might be needed before a second EBP is provided. One should consider the use of fluoroscopy or ultrasound to optimize the repeat EBP procedure and demonstrate effective delivery of the autologous blood in the epidural space.[63,109,112] No evidence exists on when to provide a second EBP after failure of the first, individual circumstances should guide the attending physician.

Sphenopalatine ganglion block (SPGB)

The parasympathetic sphenopalatine ganglion (SPG), which is located directly behind the nasal cavity, mediates intracranial vasodilation. Blocking this ganglion bilaterally with two cotton tips soaked in LA is known to reduce symptoms related to cluster headache, migraine and trigeminus neuralgia and is currently considered by some as a good alternative to an EBP in the management of patients with PDPH.[85] The simplicity of the technique is attractive and initial case series and an observational study did find that SPGB reduced PDPH symptoms and the need for an EBP.[85,122,123] Jespersen et al. could not confirm this in a prospective, blinded study comparing local anaesthetics with placebo for SPGB in 40 PDPH patients (70% women); in both groups, only 50% of patients needed a subsequent EBP.[124] Another study comparing early vs. late SPGB found that early application reduced the length of hospital stay, without any other differences, while a pilot meta-analysis on SPGB vs. other treatment modalities could not find a statistically significant difference in headache intensity or adverse effects, and concluded that more studies are needed.[125,126] In conclusion, although this is an interesting and simple procedure, evidence to date is not conclusive of its efficacy compared to placebo.

THE FUTURE

The debate on the management of PDPH following dural puncture (deliberate or inadvertent) continues. Evidence is still lacking if an early EBP, in patients with severe symptoms, also reduces the incidence of intracranial bleeding. Studies are needed that compare maximal tolerated EBP blood volume vs. a maximum of 20 ml or lower and to determine the relation between EBP volume, success rate and the occurrence of side effects, as current practice is based on only one properly designed study. The efficacy and safety of inserting an ITC once ADP occurs need to be further examined in randomized studies.[76,92] The precise mechanism by which an EBP reduces headache immediately after injection needs to be explored, transcranial Doppler can be used to determine if immediate cerebral arterial

vasoconstriction explains the prompt relief of symptoms after receiving an EBP. All future studies should document precisely, using ultrasound, the level of neuraxial procedures to study the observed association between initial ADP level, the severity of PDPH and success rates of EBPs. Do novel strategies such as a SPGB or the provision of high-flow oxygen reduce the need for an EBP in patients with severe PDPH? Finally, increased international collaboration between researchers is needed to accelerate global PDPH research and reduce the duration of clinical trials by enhancing patient recruitment. It will facilitate faster optimization of PDPH management strategies and reduce patient suffering from this iatrogenic complication of neuraxial procedures. Please see Box 7.

Box 7. Research agenda

Late vs. early application of EBP in severe PDPH
Associations between PDPH, EBP and chronic sequelae
Optimal volume of EBP
Safety and efficacy of ITC insertion during ADP to prevent severe PDPH
Underlying pathophysiology of ADP, PDPH and EBP
Ultrasound to study association between level of neuraxial procedures, PDPH and EBP
Significance of SPGB and occipital nerve block in the management of PDPH
High-flow oxygen administration and the need for EBP

CONCLUSIONS

Postdural puncture headache is an uncommon complication of neuraxial anaesthesia and analgesia, resulting from either accidental or intentional puncture of the spinal meningeal membranes, but it also occurs after other diagnostic or therapeutic neuraxial procedures. The intensity of PDPH may be severe depending on various factors, including needle size and design. It is often self-limiting and treatment may be conservative if the headache is not very severe. More severe cases are often treated with an EBP, specifically following ADP, which is successful in about 70-80% of patients after the first attempt. Some patients may need two or more EBPs before PDPH resolves, but chronic residual symptoms are not uncommon. The precise timing for performing EBP depends on the individual patient and physician but initial conservative management is common. There is a small but significant risk that unresolved PDPH after an EBP may be due to other intracranial pathology and this should be investigated early, specifically if the headache character alters. The benefit of intrathecal catheters in the prevention of PDPH needs to be further investigated and promising new therapeutic strategies explored. Patients suffer a lot as a result of PDPH and efforts should be made to provide easy access to atraumatic spinal needles worldwide. International cooperation should intensify to better understand and manage PDPH in both obstetric and non-obstetric populations.

Box 8. Practice points

- Prevention is always better than cure (avoid ADP when possible)
- Initial conservative management for 24-48 h unless symptoms are very severe, when EBP should be considered early
- Aim to administer 20 ml blood if possible during EBP
- Mobilize early, both during conservative management and after EBP
- Consider further diagnostics (CT/MRI) if the headache has an abnormal presentation or changes in character during observation
- Follow-up patients after discharge until resolution of symptoms

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Chapter 8

Management practices for postdural puncture headache in obstetrics: a prospective, international, cohort study

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ABSTRACT

Background:
Accidental dural puncture is an uncommon complication of epidural analgesia and can cause postdural puncture headache (PDPH). We aimed to describe management practices and outcomes after PDPH treated by epidural blood patch (EBP) or no EBP.
Methods: Following ethics committee approval, patients who developed PDPH after accidental dural puncture were recruited from participating countries and divided into two groups, those receiving EBP or no EBP. Data registered included patient and procedure characteristics, headache symptoms and intensity, management practices, and complications. Follow-up was at 3 months.

Results
A total of 1001 patients from 24 countries were included, of which 647 (64.6%) received an EBP and 354 (35.4%) did not receive an EBP (no-EBP). Higher initial headache intensity was associated with greater use of EBP, odds ratio 1.29 (95% confidence interval 1.19-1.41) per pain intensity unit increase. Headache intensity declined sharply at 4 h after EBP and 127 (19.3%) patients received a second EBP. On average, no or mild headache (numeric rating score ≤3) was observed 7 days after diagnosis. Intracranial bleeding was diagnosed in three patients (0.46%), and backache, headache, and analgesic use were more common at 3 months in the EBP group.

Conclusions
Management practices vary between countries, but EBP was more often used in patients with greater initial headache intensity. EBP reduced headache intensity quickly, but about 20% of patients needed a second EBP. After 7 days, most patients had no or mild headache. Backache, headache, and analgesic use were more common at 3 months in patients receiving an EBP.

INTRODUCTION

The increased availability of safe and efficacious labour epidural analgesia in the Western world has contributed to an improved birth experience for many women, as it alleviates pain during labour. Unfortunately, there is a small (0.3-1.5%) risk of iatrogenic accidental dural puncture (ADP).[1,2] If it occurs, 50-88% of women will develop symptoms of postdural puncture headache (PDPH).[2,3] From a European perspective, with 5 million babies born in the EU in 2017 and an epidural labour analgesia rate between 20% and 80%, ADP results in approximately 10 000-15 000 women developing PDPH every year.[4] This may cause impaired ability to self-mobilise and breastfeed the baby, delays hospital discharge,[5] and sometimes chronic headache and backache may develop.[6] Also, a small but statistically significant increase in the incidence of intracranial bleeding (ICB) has been described in patients with PDPH, compared with those without a headache.[7] Therefore, ADP and subsequent PDPH add a cost and resource burden to an already strained healthcare system in Europe. Different management strategies for PDPH exist, ranging from conservative management to treatment with an epidural blood patch (EBP). So far, the best interventional therapy that has been demonstrated to immediately reduce the severity and duration of PDPH is an EBP.[8,9] Although EBPs are efficacious, some patients may experience rebound headache requiring a new EBP.[10] However, only limited evidence exists from small prospective randomised trials and systematic reviews as to the choice between continuing conservative management or applying an EBP for management of PDPH. Therefore, the aims of this multinational cohort study were to describe characteristics of PDPH and its management, to describe and identify factors related to physician treatment choices in the application of EBP or not, to describe intensity of headache over time in patients treated with EBP or no-EBP, and to record any complication after EBP or conservative management.

METHODS

This was a prospective, multicentre, international, pragmatic, observational, cohort study where 158 centres from 27 countries registered to participate. Data were collected during the period January 1, 2016, to December 31, 2018. The ethical committee in the countries/institutions approved the study and it was registered in clinicaltrials.gov (NCT: 02362828).

Signed, informed consent was obtained from each patient before inclusion if the ethics committee in the country/hospital stated this to be mandatory. All consenting women ≥18 yr admitted to the hospital and having epidural analgesia during labour were included in the study if confirmed/suspected ADP occurred and a clinical diagnosis of PDPH was made postpartum. When a combined spinal-epidural technique was used during labour or Caesarean section, CSF had to be seen in the epidural needle and PDPH had to occur to include the patient into the study. Exclusion criteria were: hospitals performing <500 deliveries/yr, patients having PDPH after spinal anaesthesia alone, no definite evidence of ADP observed at epidural insertion when performing a combined spinal-epidural anaesthesia/

analgesia, language constraints, any medical disorder which may prevent compliance with the protocol, and patients presenting with PDPH >5 days after epidural anaesthesia or analgesia. At each site, a specialist anaesthesiologist evaluated the patients with a demonstrated/suspected ADP and characteristic symptoms of PDPH after epidural anaesthesia or analgesia, to confirm the diagnosis (definition below).[11] Headache intensity was measured using a numeric rating score (NRS) where 0=no pain and 10=worst imaginable pain. General data protection regulation guidelines were followed and patient and procedure characteristics, location of headache, and management strategies were collected through an internet-based program (OpenClinica). Patients recruited into the study were followed up until discharge from the hospital and subsequently at home at 3 months by telephone. Any readmission as a result of PDPH/EBP was recorded until 3 months.

Definitions

ADP was defined as visible CSF in the epidural needle, a positive aspiration test through an epidural catheter, or typical evidence of spinal anaesthesia after injection of local anaesthetic via the epidural catheter.
PDPH was defined as:[12]

1. Headache that worsens within 15 min after sitting or standing and improves within 15 min after lying down after dural puncture has occurred or is suspected.
2. The headache develops within 5 days after dural puncture (confirmed or possible).
3. The headache may or may not be accompanied by neck stiffness, vestibular, visual, or auditory symptoms.

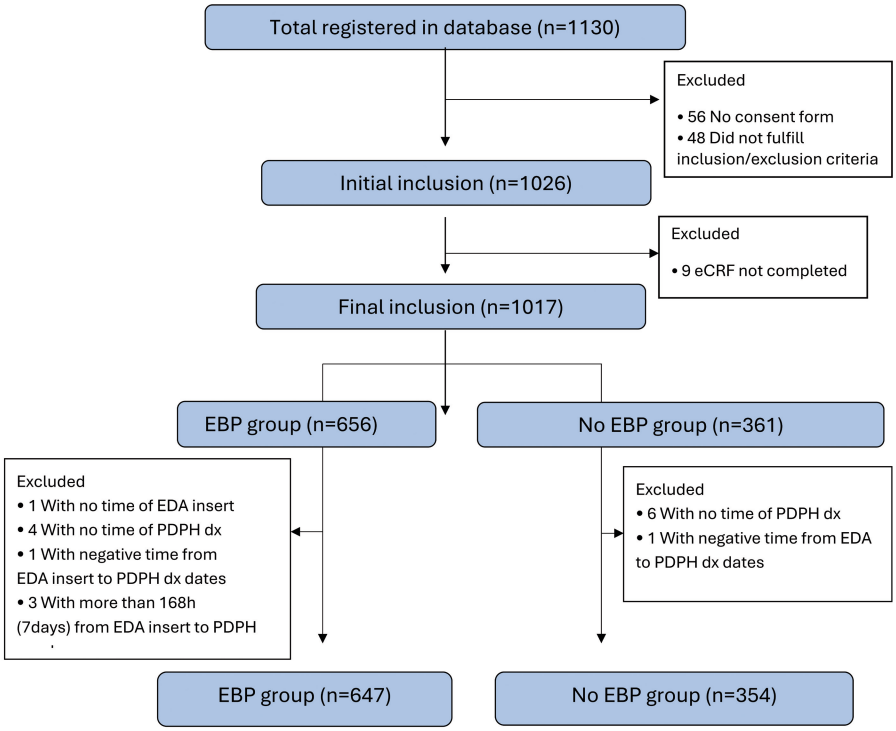
Persistent backache or headache was defined as NRS ≥3 at 3 months.

Spontaneous recovery of headache was defined as NRS<3 sitting/standing up at 24 h after PDPH diagnosis NRS<3 within 24 h after PDPH diagnosis.

PDPH with minimal orthostatic component was defined as a headache with <2 points difference in intensity on the NRS scale when comparing standing/sitting with lying position.

The European Society of Anaesthesiology was the sponsor and coordinated the study. The sponsor was responsible for implementing and maintaining quality assurance and quality control systems to ensure that the trial was conducted, and data were generated, documented, and reported in compliance with the protocol, Good Clinical Practice, and the applicable local regulatory requirements. Verification of data quality and registration was the responsibility of the local principal investigator, which was controlled by the sponsor with random assessments of centres to confirm correctness of data entered.

Fig 1. STROBE diagram for patient recruitment and data analyses.



Abbreviations: Dx, diagnosis; EBP, epidural blood patch; eCRF, electronic case record form; EDA, epidural analgesia; PDPH, postdural puncture headache.

Statistics

An unpaired t-test was used to compare continuous variables, the Mann-Whitney test was used to compare skewed variables, and the χ^2 test or Fischer exact test was used to compare categorical variables between EBP and no-EBP groups. Unless otherwise stated, results of NRS score (headache and backache) are presented in the sitting/upright position.

A stepwise logistic regression was used to identify independent variables to the choice of EBP/no-EBP treatment. All variables in Tables 1-3 were potential independent variables and modelled as categorical variables together with NRS pain intensity at diagnosis of PDPH as a continuous variable, and the significance level for the selection criteria was set to 0.20. This analysis was performed with full data available (complete cases), which resulted in 603 EBP and 342 no-EBP patients (total 945 patients).

Unadjusted and adjusted linear regression was used to evaluate the change in NRS pain intensity from PDPH diagnosis to 0-24 h, 7 days, and at 3 months post PDPH diagnosis between EBP and no-EBP groups. The adjusted models were further adjusted for NRS pain intensity at PDPH diagnosis, country of recruitment, and using a stepwise procedure with selection criteria 0.20 to adjust for independent variables to the outcome among the variables in Tables 1-3. As the mean pain intensity at PDPH diagnosis was different in the EBP and no-EBP groups, only patients with NRS ≥7 (resulting in 764 patients) and with complete information on all variables in Tables 1-3 were considered, resulting in 719 patients (498 EBP and 221 no-EBP patients). As there were missing outcome data on NRS pain intensity post PDPH diagnosis, the analysis was performed on the number of patients indicated in Table 4. To try to compensate for the missing outcome data, the adjusted models were also evaluated with the multiple imputation chained equations technique using the same variables for the imputation as were selected in the adjusted models described above. Statistical significance level was set to two-sided 5% and STATA release 14 and SPSS version 24 were used for the statistical computations.

RESULTS

A total of 1130 patients were included between January 2016 and December 2018 from 24 participating countries. However, after a complete data assessment, 1001 patients were included in the final analyses; 647 (64.6%) in the EBP group and 354 (35.4%) in the no-EBP group (Fig. 1). The distribution of the total number and percentage of patients who had EBP across the countries is shown in Figure 2. Fewer than 50% patients received an EBP in Spain, Portugal, Greece, and Italy.

Table 1. Patient characteristics and headache pain intensity as numeric rating score (NRS) on sitting up at the time of PDPH diagnosis.

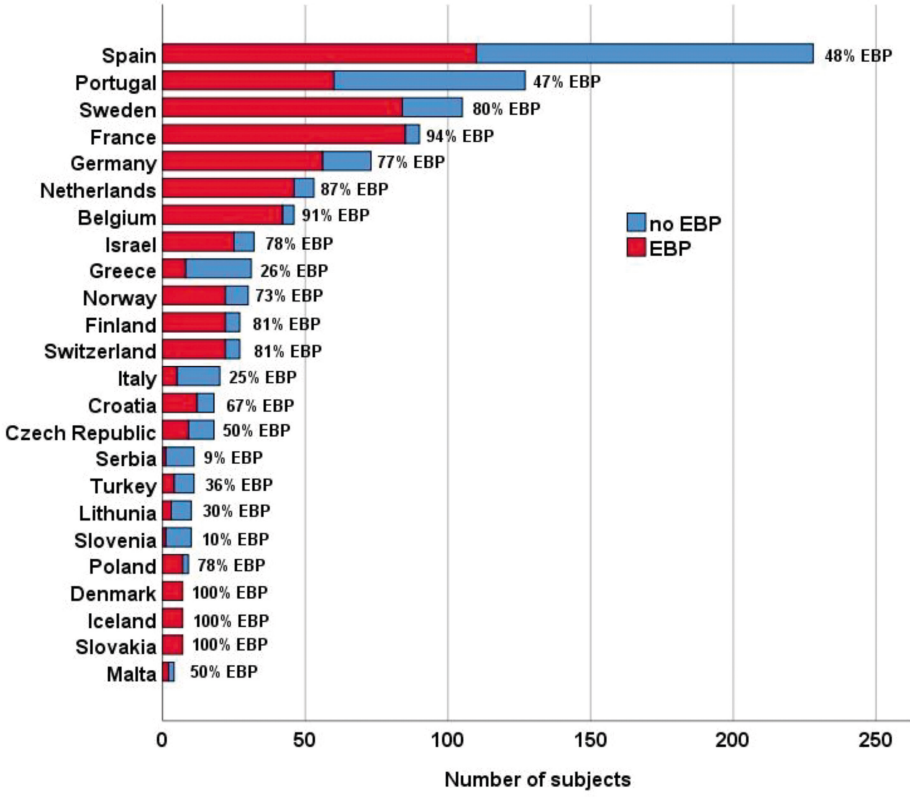
	Total (n=1001)	EBP (n=647)	No-EBP (n=354)	*P*-value
Mother's age				
Mean (SD, range)	31.0 (5.1. 18-46)	31.0 (4.9. 18-46)	31.0 (5.6. 18-44)	0.9
Parity				
Multipara, n (%)	510 (51)	337 (52)	173 (49)	0.33
BMI (kg/m^2)	(n=1000)	(n=646)	(n=354)	
Mean (SD)	27.7 (5.5)	27.4 (5.2)	28.1 (6.0)	0.077
Previous history, n (%)				
Neuraxial anaesthesia	266 (26)	162 (25)	104 (29)	0.14
Postdural puncture headache	31 (3)	17 (3)	14 (4)	0.25
Chronic headache	40 (4)	30 (5)	10 (3)	0.16

Table 1. Continued

	Total (n=1001)	EBP (n=647)	No-EBP (n=354)	*P*-value
Migraine	139 (14)	98 (15)	41 (12)	0.12
Vertebral column pathology	81 (8)	49 (8)	32 (9)	0.42
Chronic backache	61 (6)	41 (6)	20 (6)	0.66
Smoker	(n=1000)	(n=646)	(n=354)	
Yes, n (%)	119 (12)	64 (10)	55 (16)	0.009
Occupation, n (%)				
Administration	135 (13)	93 (14)	42 (12)	0.27
Teaching	81 (8)	60 (9)	21 (6)	0.064
Healthcare	147 (15)	110 (17)	37 (10)	0.005
Professional worker (no university education)	216 (22)	125 (19)	91 (26)	0.019
Professional worker (with university education)	214 (21)	149 (23)	65 (18)	0.085
None	208 (21)	110 (17)	98 (28)	<0.001
Highest education, n (%)	(n=998)	(n=645)	(n=353)	
Basic schooling	172 (17)	89 (14)	83 (24)	<0.001
High school	384 (38)	245 (38)	139 (39)	0.67
University	442 (44)	311 (48)	131 (37)	0.001
Mode of delivery, n (%)				
Spontaneous	688 (69)	455 (70)	233 (66)	0.14
Instrumental	120 (12)	79 (12)	41 (12)	0.77
Caesarean section	193 (19)	113 (17)	80 (23)	0.049

Abbreviations: EBP, epidural blood patch; PDPH, postdural puncture headache; SD, standard deviation.

Fig 2. The number of patients recruited from each country and percentage of epidural blood patches (EBP) performed.



Characteristics of patients and epidurals

Characteristics of patients, equipment, and methods used for performing epidurals in all patients are shown in Table 1. Patients in the EBP group had a significantly higher level of education, were more often healthcare workers, non-smokers, and had fewer Caesarean section deliveries compared with the no-EBP group. Characteristics of epidural technique, diagnostic symptoms and their location and management of PDPH are shown in Table 2. In 41% of patients ADP was diagnosed by classical signs of PDPH, without CSF in needle/catheter. An intrathecal catheter (ITC) was inserted after ADP in 18% of patients; 14% in EBP vs 25% in the no-EBP group, $P<0.001$. Significantly more patients could breastfeed in the no-EBP group (94% vs 84%, $P<0.001$).

Table 2. Characteristics of epidural technique, PDPH diagnosis, and management of PDPH.

	Total (n=1001)	EBP (n=647)	No-EBP (n=354)	*P*-value
Needle size, n (%)				
16G	63 (6)	40 (6)	23 (6)	0.84
17G	101 (10)	87 (13)	14 (4)	<0.001
18G	820 (82)	507 (78)	313 (88)	<0.001
19-20G	17 (2)	13 (2)	4 (1)	0.3
Media for detecting loss of resistance, n (%)	(n=1000)	(n=646)		
Air	169 (17)	71 (11)	98 (28)	<0.001
Saline	816 (82)	564 (87)	252 (71)	<0.001
Both	15 (2)	11 (2)	4 (1)	0.48
Position of patient inserting epidural, n (%)		(n=644)		
Lying	177 (18)	124 (19)	53 (15)	0.09
Sitting	821 (82)	520 (81)	301 (85)	
Level of insertion epidural, n (%)	(n=1000)	(n=646)		
L1-2	55 (6)	38 (6)	17 (5)	0.48
L2-3	255 (25)	184 (28)	71 (20)	<0.001
L3-4	557 (56)	338 (52)	219 (62)	0.003
L4-5	133 (13)	86 (13)	47 (13)	>0.99
Technical difficulties inserting epidural, n (%)	326 (33)	203 (31)	123 (35)	0.28
Multiple attempts inserting epidural, n (%)	452 (45)	307 (47)	145 (41)	0.049
Duration (h), median (IQR)				
Epidural insertion to PDPH diagnosis	31.0 (21.0-51.5)	32.7 (21.0-53.7)	29.9 (20.8-48.0)	0.02
Epidural insertion to EBP	NA	(n=646)	68.4 (47.7-96.8)	NA
Intrathecal catheter placed after ADP, n (%)	181 (18)	91 (14)	90 (25)	<0.001
Operator experience, n (%)				
<6 months	103 (10)	74 (11)	29 (8)	0.11
6 months to 1 yr	92 (9)	68 (11)	24 (7)	0.051
1-5 yr	400 (40)	244 (38)	156 (44)	0.05
>5 yr	406 (41)	261 (40)	145 (41)	0.85

Table 2. Continued

	Total (n=1001)	EBP (n=647)	No-EBP (n=354)	*P*-value
How was ADP determined, n (%)				
CSF in epidural needle	509 (51)	323 (50)	186 (52)	0.43
CSF in catheter/positive aspiration test	112 (11)	60 (9)	52 (15)	0.009
Spinal anaesthesia after test dose	96 (10)	56 (9)	40 (11)	0.17
Classical signs PDPH postpartum	408 (41)	291 (45)	117 (33)	<0.001
Other symptoms (addition to classical PDPH), n (%)				
Nausea/vomiting	221 (22)	158 (24)	63 (18)	0.016
Auditory symptoms	179 (18)	142 (22)	37 (10)	<0.001
Diplopia	18 (2)	15 (2)	3 (1)	0.094
Dizziness	240 (24)	162 (25)	78 (22)	0.29
Any other visual symptoms	126 (13)	90 (14)	36 (10)	0.088
Tinnitus	103 (10)	74 (11)	29 (8)	0.11
Other	155 (15)	108 (17)	47 (13)	0.15
Patient sent home before symptoms first presented, n (%)	80 (8)	61 (9)	19 (5)	0.023
Breastfeeding despite PDPH, n (%)	(n=954) 840 (88)	(n=611) 516 (84)	(n=343) 324 (94)	<0.001
Location of the headache, n (%)				
Temporal	243 (24)	182 (28)	61 (17)	<0.001
Occipital	571 (57)	386 (60)	185 (52)	0.024
Frontal	662 (66)	441 (68)	221 (62)	0.067
Neck	628 (63)	437 (68)	191 (54)	<0.001
Shoulder	234 (23)	163 (25)	71 (20)	0.066
Other	37 (4)	28 (4)	9 (2)	0.15
Type of conservative treatment before diagnosis, n (%)				
Paracetamol	654 (65)	462 (71)	192 (54)	<0.001
NSAID	521 (52)	356 (55)	165 (47)	0.011
Caffeine	249 (25)	166 (26)	83 (23)	0.44
Opioids	113 (11)	85 (13)	28 (8)	0.012
Fluids	339 (34)	225 (35)	114 (32)	0.41
Bed rest	363 (36)	244 (38)	119 (34)	0.2

Abbreviations: ADP, accidental dural puncture; EBP, epidural blood patch; IQR, inter-quartile range; PDPH, postdural puncture headache.

Results of stepwise logistic regression analysis are shown in Table 3. The following interesting factors were independently associated with a greater chance of receiving an EBP: pain intensity at diagnosis (odds ratio [OR] 1.29 per unit NRS increase), 17 G epidural needle (OR 5.43 compared with 18G), auditory symptoms (OR 1.64), and multiparity (OR 1.72). Interesting factors independently associated with a greater chance of not receiving an EBP were use of air as the medium for detecting loss of resistance (LoR) (OR 0.45), catheter placed intrathecally after ADP (OR 0.53), and a previous history of PDPH (OR 0.36).

Table 3. Results of stepwise logistic regression to identify independent variables for outcome EBP treatment choice (yes/no).

	OR (95%CI)	*P*-value
NRS pain intensity at PDPH, per unit	1.29 (1.19-1.41)	<0.001
Type of conservative treatment before diagnosis		
Paracetamol	1.90 (1.34-2.68)	<0.001
Caffeine	0.74 (0.49-1.10)	0.13
Media for detecting loss of resistance		
Air	0.45 (0.29-0.67)	<0.001
Saline	Ref	
Both	1.36 (0.33-5.58)	0.67
Catheter placed intrathecally after ADP	0.53 (0.36-0.78)	0.001
Needle size		
16G	0.92 (0.47-1.82)	0.82
17G	5.43 (2.64-11.1)	<0.001
18G	Ref	
19-20G	2.62 (0.61-11.3)	0.2
Occupation		
Administration	1.15 (0.70-1.90)	0.58
Teaching	1.03 (0.56-1.92)	0.91
Healthcare	1.47 (0.89-2.42)	0.13
Professional worker	Ref	
None	0.62 (0.40-0.96)	0.034
Breastfeeding despite PDPH	0.43 (0.24-0.76)	0.004
Location of the headache		
Temporal	1.59 (1.08-2.35)	0.019
Occipital	1.27 (0.91-1.75)	0.16
Frontal	1.57 (1.11-2.20)	0.01

Neck	1.50 (1.08-2.08)	0.014
Other	2.84 (1.13-7.11)	0.026
Other symptoms (addition to classical PDPH)		
Auditory symptoms	1.64 (1.05-2.56)	0.031
Medical history		
Neuraxial anaesthesia	0.73 (0.48-1.10)	0.13
PDPH	0.36 (0.14-0.88)	0.026
Chronic headache	1.93 (0.76-4.91)	0.17
Multipara	1.72 (1.18-2.51)	0.005
Patient sent home before symptoms first presented	1.88 (0.98-3.59)	0.056
Smoker	0.63 (0.39-1.02)	0.061
Level of insertion of epidural		
L1-2	1.18 (0.56-2.48)	0.66
L2-3	1.75 (1.18-2.61)	0.006
L3-4	Ref	
L4-5	1.22 (0.74-1.99)	0.43
Highest education		
Basic schooling	0.65 (0.39-1.08)	0.093
High school	0.64 (0.44-0.93)	0.019
University	Ref	
Mother's age (yr)		
≤24	0.88 (0.50-1.55)	0.66
25-29	1.11 (0.73-1.69)	0.63
30-34	Ref	
≥35	0.71 (0.48-1.05)	0.087

The potential independent variables were the patient characteristics variables (Table 1), the epidural technique variables and the PDPH symptoms and diagnosis variables (Table 2), and NRS intensity of headache at PDPH diagnosis.
Significance level for the variable selection criteria was 0.20. Complete cases analyses resulted in 945 subjects (603 EBP and 342 no-EBP). OR>1 indicates more patients to EBP treatment for the exposed category compared with nonexposed/reference.
Abbreviations: ADP, accidental dural puncture; CI, confidence interval; EBP, epidural blood patch; NRS, numeric rating score; OR, odds ratio; PDPH, postdural puncture headache.

Headache location, intensity, and time course

The location of the headache is shown in Table 2 and the intensity of headache at the time of diagnosis in different countries is shown in Supplementary table 1S. PDPH with only a minimal orthostatic component was reported by a total of 6.4% patients (8.8% vs 5.1% in the no-EBP vs the EBP group, P=0.024). The overall mean headache intensity (NRS, 0-10) was significantly higher in the EBP group, mean 8.0 (SD 1.8) compared with the no-EBP group, mean 6.9 (SD 2.3). Excluding Spain (that recruited many patients) from the analyses did not change the findings. Spontaneous recovery of headache after PDPH diagnosis and within 24 h occurred in 5.8% patients (12.2% vs 2.2% in the no-EBP vs the EBP group, P<0.001). The intensity of headache decreased significantly from PDPH diagnosis to 4 h after application of the EBP (mean 8.0 vs 1.5, P<0.001) (Fig. 3). However, 67/640 (10.5%) had a return of headache (NRS ≥7) within 24 h after the first EBP. On average, patients in both groups had mild headache (NRS<3) after 7 days. When assessing all patients with severe headache at diagnosis (NRS ≥7), a significantly greater spontaneous reduction in NRS pain intensity from PDPH diagnosis was seen in favour of the no-EBP group compared with the EBP group within 24 h (adjusted mean difference 1.4, P<0.001) and after 7 days in favour of the EBP group (adjusted mean difference -1.0, P<0.001), but no significant difference was seen after 3 months (adjusted mean difference 0.2, P=0.23) (Table 4). These significant findings remained essentially the same with multiple imputation.

Table 4. Linear regressions comparing change in NRS pain intensity from PDPH diagnosis to 0-24 h, 7 days, and 3 months.

	NRS pain PDPH dx		NRS pain 0-24 h		Change of NRS pain				
	n	Mean (SD)	n	Mean (SD)	Mean change	Unadjusted (95% CI)	*P*-value	Adjusted*,†,§ (95% CI)	*P*-value
No-EBP	212	8.3 (1.1)	212	6.7 (2.6)	-1.5	Reference		Reference	
EBP	486	8.6 (1.1)	486	8.5 (1.7)	-0.1	1.4 (1.1-1.7)	<0.001	1.4 (1.0-1.7)	<0.001
	NRS pain PDPH dx		NRS pain 7 days		Change of NRS pain				
	n	Mean (SD)	n	Mean (SD)	Mean change	Unadjusted (95% CI)	*P*-value	Adjusted*,‡,§ (95% CI)	*P*-value
No-EBP	202	8.3 (1.1)	202	1.8 (2.4)	-6.5	Reference		Reference	
EBP	420	8.6 (1.1)	420	1.0 (2.0)	-7.6	-1.1 (-1.5 to -0.7)	<0.001	-1.0 (-1.4 to -0.6)	<0.001
	NRS pain PDPH dx		NRS pain 3 months		Change of NRS pain				
	n	Mean (SD)	n	Mean (SD)	Mean change	Unadjusted (95% CI)	*P*-value	Adjusted*,¶,§ (95% CI)	*P*-value
No-EBP	145	8.3 (1.1)	145	0.2 (0.7)	-8.2	Reference		Reference	
EBP	311	8.6 (1.1)	311	0.5 (1.7)	-8.1	0.1 (-0.2 to 0.4)	0.56	0.2 (-0.1 to 0.5)	0.23

Unadjusted and adjusted for NRS pain intensity at PDPH diagnosis, country, and other background variables selected from stepwise procedure (see statistical methods for details). Only subjects with complete information on NRS pain intensity, the background variables, and having NRS pain intensity ≥7 at PDPH diagnosis were included.

Abbreviations: ADP, accidental dural puncture; CI, confidence interval; dx, diagnosis; EBP, epidural blood patch; NRS, numeric rating score; OR, odds ratio; PDPH, postdural puncture headache; SD, standard deviation.

Notes for table 4:

** Adjusted for NRS pain intensity at PDPH and country of residence.*

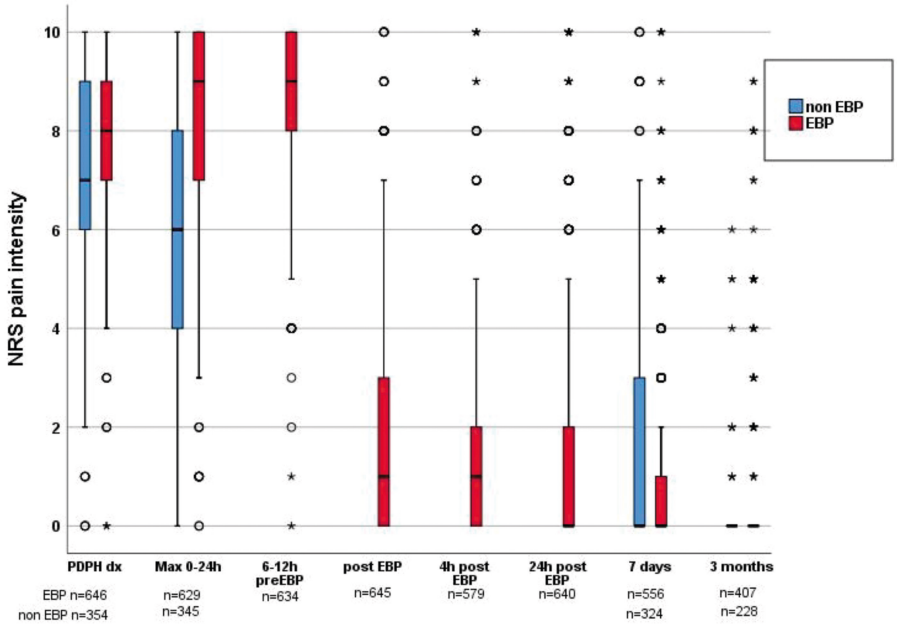
† Adjusted also for mother's BMI, occipital location of the headache at PDPH dx, other location of the headache at PDPH dx, patient sent home when first PDPH symptoms present, bedrest as conservative treatment before PDPH diagnosis, besides classical PDPH symptoms also nausea/vomiting symptoms present, besides classical PDPH symptoms also dizziness symptoms present, ADP was determined as classical signs of PDPH postpartum, ADP was determined as CSF in catheter or positive aspiration test, neuraxial anaesthesia as medical history, migraine as medical history, mother's occupation, and mode of delivery.

‡ Adjusted also for catheter placed intrathecally after ADP, besides classical PDPH symptoms also diplopia symptoms present, mode of delivery, temporal location of the headache at PDPH dx, neck location of the headache at PDPH dx, PDPH as medical history, and chronic backache as medical history.

¶ Adjusted also for neck location of the headache at PDPH dx, mother can breastfeed her child, air or saline media for detecting loss of resistance, PDPH as medical history, occipital location of the headache at PDPH, smoking, education level, paracetamol as conservative treatment before PDPH diagnosis, besides classical PDPH symptoms also diplopia symptoms present, multiple attempts at inserting epidural needle at different levels.

§ Results from multiple imputation, adjusted NRS pain mean change from PDPH to 0-24 h 1.3 (95% CI 1.0 to 1.6) P<0.001, to 7 days -1.1 (95% CI -1.5 to -0.7) P<0.001 and to 3 months 0.1 (95% CI -0.2 to 0.4) P=0.54.

Fig 3. Boxplot showing NRS pain intensity from PDPH diagnosis to 3 months in EBP and no-EBP groups.



In the EBP group, a significant decrease in NRS pain intensity was found from pre-to post-EBP (P<0.001). The horizontal line in the box represents the median, the boxes inter-quartile range (IQR) and the whiskers min and max if no outlier present; outliers >1.5 times IQR are indicated as circles, outliers >3 times IQR are indicated as asterisks.
Abbreviations: dx, diagnosis; EBP, epidural blood patch; NRS, numeric rating score; PDPH, postdural puncture headache.

Management of PDPH after diagnosis

The median (IQR) time from epidural insertion to PDPH diagnosis was 31 (21-51.5) h and to EBP was 68.4 (47.7-96.8) h (Table 2). Other characteristics of epidural technique, diagnosis and management are also shown in Table 2. Sphenopalatine and/or occipital nerve block was performed in 3.3% patients, mostly from Portugal. From a total of 647/1001 (64.6%) who received an EBP, 127 women (19.6%) received a second blood patch because of recurrence of headache, and a further seven women (1.1%) received a third blood patch. When EBP was performed in <24 h from the PDPH diagnosis, a significantly greater number of patients received a second EBP (77/314, 24%) compared with when EBP was performed >24 h (50/321, 15%), P=0.002.

Complications of epidurals, ADP and EBP

A total of 47/647 (7.3%) patients in the EBP group were further examined after failure of an EBP and 39/47 underwent CT/MRI examination. Five patients (0.8%) had the following

important findings: ICB (n=3), minimal subdural hematoma (n=1) (all seen on CT/MRI), intrathecal bleeding accompanied by the syndrome of reversible vasoconstriction (n=1) (seen on Doppler ultrasound), and probable aseptic meningitis (n=1) (classical symptoms with negative bacterial growth in CSF). Of the 635 patients (407 in the EBP group and 228 in the no-EBP group) who were followed up at 3 months, persistent backache was the commonest symptom reported by 14% (17% vs 8.8% in the EBP and no-EBP groups, respectively, P=0.004); the results continued to be statistically significant after excluding patients who had chronic backache before delivery (14.6% vs 7.5%, P=0.01). Persistent headache (NRS ≥3) at 3 months was reported by 5.0% patients (6.9% vs 1.7% in the EBP and no-EBP group, respectively, P<0.001). The commonest other symptoms included neck stiffness, auditory and visual symptoms, and nausea. In all, 10.1% patients were receiving medication (12.0% in EBP group and 6.6% in no-EBP group, P=0.028) for either headache or backache at 3 months.

DISCUSSION

ADP during initiation of epidural labour analgesia often causes PDPH affecting >10 000 women in Europe each year and affects postpartum maternal well-being, maternal-neonatal bonding and breastfeeding, and may delay hospital discharge. In this international, prospective, multicentre, cohort study, we were interested in determining the current practices in the management of PDPH, the factors that led the physician to choose between the application of EBP or conservative treatment only, and the outcome after 3 months for patients treated by EBP or conservatively. We found that, although EBP was the preferred method for management of PDPH, it was performed less frequently (<50%) in Spain, Portugal, Italy, and Greece. The precise explanation for this difference in observed practice between countries remains unclear from the present study, but institutional guidelines, obstetric anaesthesia practices, and individual physician preference may have contributed to these differences.[13]

Factors associated with conservative management (no-EBP) were the use of an ITC after ADP and the use of air as a medium for detection of LoR. There is mixed evidence from the literature regarding leaving an ITC in place after ADP on subsequent development of PDPH and the reduced need for an EBP.[14-16] This could be because of local inflammation or plugging of the dural hole which reduces CSF leakage, but this needs to be further evaluated in prospective, randomised studies.[17,18]

The use of air or saline for detection of LoR remains controversial, but a recent Cochrane review found no difference in several endpoints, including PDPH, using either technique.[19] Accidental injection of air intrathecally results in an almost immediate onset of PDPH (<1 h), with a shorter duration compared with PDPH after using saline for LoR.[20] This rapid onset and faster recovery of headache may explain the reduced application of an EBP for management of PDPH after the use of air for LoR.

Factors significantly related to physician choice for EBP included increasing intensity of PDPH after initial diagnosis (NRS ≥7), use of a larger gauge epidural needle (<18G), headache presenting dominantly in the frontotemporal or neck region, multiparity, and the presence of auditory symptoms. The intensity of headache is often a determining factor in treatment choice, which is confirmed in this study with stepwise regression analysis demonstrating the odds of receiving an EBP increase per unit increase in NRS headache intensity at PDPH diagnosis. Indeed, guidelines in France recommend that conservative management without EBP should preferably be used when the intensity of PDPH is mild to moderate.

Localisation of headache and the presence of auditory symptoms may influence the physician choice. It has been demonstrated before that large diameter epidural needles cause more severe headaches. The increased use of EBP in multiparous women is intriguing. It is likely that multiparas mobilise earlier, causing a more severe headache because of increased CSF leakage and therefore an increased use of EBP. One study, however, found that earlier mobilisation did not lead to more severe headache.[21]

In our present study, headache intensity declined significantly within 4 h after application of an EBP, which is important from a patient perspective. The speed of decline in the no-EBP group after the first 24 h is unknown, as we did not assess headache intensity daily. In both groups, headache at 7 days was, on average, either absent or mild (NRS<3).

When assessing patients with only severe PDPH (NRS ≥7) at diagnosis and comparing the EBP group and the no-EBP group, we found a small but statistically significant mean difference of 1 NRS unit in favour of the EBP group at 7 days. The clinical relevance of this small difference is disputable. In agreement with previous studies we found that about one in five patients had a recurrence of headache 24-48 h after the initial EBP requiring the application of a new EBP.[22] The reasons for this and an analysis of failure of EBP are not within the scope of the present study, but will be discussed in a later sub-analysis of data from European Practices in the Management of Accidental Dural Puncture (EPiMAP).

Towards the end of recruitment in 2018, some case reports and series were published describing the use of sphenopalatine ganglion or occipital nerve block as a management strategy for PDPH with favourable results.[9] Unfortunately, in our present study, there were very few cases reported since it was not an obligatory question, and mostly from Portugal, and therefore it is difficult to make any definite conclusions based on this data. Further studies are keenly awaited on this method of management of PDPH.

It is important to study the complications that may arise from administration of an EBP compared with conservative treatment. Although EBP is clearly efficacious, fear remains that its application may cause a new ADP, the headache may not resolve or there may be serious or persistent complications. In our study, five patients had serious complications, three of them being ICB, which were all identified in the EBP group (5 of 647 patients, 0.46%) when further

diagnostic methods such as CT/MRI were applied after the first or second EBP failure. These results are comparable to the known increased incidence of ICB in obstetric PDPH patients, but the relation with the EBP is not clear.[23] PDPH which does not recover spontaneously or after EBP, change character, or if there are new focal neurological signs should arouse suspicion of an intracranial complication and neuro-imaging, should then be considered.

Patients receiving an EBP showed a statistically higher incidence of chronic headache and backache and an increased use of analgesics at 3 months, compared with the no-EBP group. This finding contradicts results from several retrospective case-control series, which reported lower or unchanged incidences in patients who received an EBP.[24,25] The overall incidence of both chronic headache and backache was lower though in our prospective cohort, which measured only moderate to severe headache (NRS≥3) instead of any headache or backache.

STUDY LIMITATIONS

Although the data presented are robust and the conclusions meaningful, many countries and centres were involved in data collection, and there may be physician or centre bias in patient management. We did not enquire about headache intensity each day during the first 7 days, which did not allow comparisons of headache dynamics over time between the EBP and no-EBP group. The results of maximal headache intensity 0-24 h after PDPH diagnosis (shown in Fig. 3 and Table 4) should be interpreted with caution because only half the patients had received an EBP within 24 h after PDPH diagnosis and the maximum 0-24 h intensity was assessed. Since this is a cohort study, the EBP intervention was not randomised, and therefore the mean pain intensity comparison between the EBP and no-EBP groups over time should be interpreted with some caution. The diagnostic criteria for PDPH also changed during the study period. The description of the orthostatic component of PDPH changed from 'headache that worsens within 15 min of sitting/standing and improves within 15 min of lying down' to 'usually but not invariably orthostatic and therefore cannot be relied upon as the diagnostic criteria'.[12,26] However, we used the criteria suggested by Amorim and colleagues[11] in 2012, which were based on the diagnostic criteria of PDPH by the International Headache Society from 2004. Another limitation of our study is that we did not collect baseline data on the number of epidurals performed, the actual number of dural punctures during the study period (including patients not recruited into the study), or the clinical course of patients having an ADP but not developing PDPH. Although these data would be interesting to determine the precise incidence of PDPH in different countries, they may not add any further relevant information regarding risk factors, management, and time course of PDPH. Finally, we did not include smaller centres (<500 deliveries/year) since experience in performing EBP at these centres may be limited.

CONCLUSIONS

In this pragmatic, observational study, 65% of patients received an EBP with large geographical variation. A greater headache intensity appeared to favour application of EBP by physicians, while the use of an ITC favoured a conservative approach. Patients treated with an EBP had rapid relief of symptoms, but about one in five patients required a second EBP. Almost all

patients had only mild headache at 7 days. Intracranial bleeding occurred in three patients and, although rare, should be a differential diagnosis in non-resolving headaches.

SUPPLEMENTARY DATA

Table 1S. Intensity of headache in different countries at the time of post-dural puncture headache (PDPH) diagnosis is shown.

Country	Total (n=1001)		EBP (n=647)		Non-EBP (n=354)		*P*-value
	n	Mean NRS (SD)	n	Mean NRS (SD)	n	Mean NRS (SD)	
Spain	228	7.6 (2.1)	110	8.1 (1.6)	118	7.1 (2.3)	<0.001
Portugal	127	7.3 (1.9)	60	7.7 (1.8)	67	7.0 (2.0)	0.035
Sweden	105	7.9 (1.8)	84	8.1 (1.8)	21	7.0 (1.9)	0.017
France	90	7.6 (2.2)	85	7.8 (2.0)	5	4.6 (2.1)	0.001
Germany	73	7.6 (1.7)	56	7.7 (1.7)	17	7.2 (1.8)	0.29
Netherlands	53	8.0 (2.1)	46	8.0 (2.2)	7	8.0 (1.3)	0.96
Belgium	46	8.0 (1.8)	42	8.2 (1.7)	4	6.5 (1.9)	0.064
Israel	32	8.4 (1.9)	25	8.8 (1.1)	7	6.8 (3.2)	0.013
Greece	31	7.0 (2.5)	8	7.2 (2.0)	23	6.9 (2.7)	0.72
Norway	30	7.5 (1.9)	22	7.6 (2.2)	8	7.1 (0.6)	0.52
Finland	27	8.1 (1.5)	22	8.1 (1.6)	5	8.0 (1.2)	0.86
Switzerland	27	8.4 (1.6)	22	8.5 (1.6)	5	7.8 (1.8)	0.38
Italy	30	7.4 (2.0)	5	9.4 (0.5)	15	6.7 (1.8)	0.003
Croatia	18	7.7 (2.5)	12	8.7 (1.4)	6	5.7 (3.1)	0.012
Czech Rep	18	6.9 (1.6)	9	7.1 (1.6)	9	6.8 (0.5)	0.67
Serbia	11	8.4 (1.4)	1	7.0 (0.0)	10	8.5 (1.4)	NA
Turkey	11	7.9 (2.0)	4	8.5 (1.3)	7	7.6 (2.3)	0.48
Lithuania	10	4.3 (2.9)	3	7.7 (1.2)	7	2.8 (2.0)	0.006
Slovenia	10	5.9 (2.8)	1	7.0 (0.0)	9	5.8 (3.0)	NA
Poland	9	7.1 (2.0)	7	7.8 (1.2)	2	4.5 (2.1)	0.019
Denmark	7	8.1 (1.8)	7	8.1 (1.8)	0	NA	NA
Iceland	7	7.4 (1.7)	7	7.4 (1.7)	0	NA	NA
Slovakia	7	8.1 (1.3)	7	8.1 (1.3)	0	NA	NA
Malta	4	7.0 (1.8)	2	7.0 (1.4)	2	7.0 (2.8)	>0.99
All patients	1.001	7.6 (2.0)	647	8.0 (1.8)	354	6.9 (2.3)	<0.001

Abbreviations: NRS, numeric rating scale; SD, standard deviation.

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Chapter 9

Factors associated with failed epidural blood patch after accidental dural puncture in obstetrics: a prospective, multicentre, international cohort study

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ABSTRACT

Background

Epidural blood patch is commonly used for management of post-dural puncture headache after accidental dural puncture. The primary aim was to determine factors associated with failed epidural blood patch.

Methods

In this prospective, multicentre, international cohort study, parturients ≥18 yr receiving an epidural blood patch for treatment of post-dural puncture headache were included. Failed epidural blood patch was defined as headache intensity numeric rating scale (NRS) score ≥7 in the upright position at 4, 24, or 48 h, or the need for a second epidural blood patch, and complete success by NRS=0 at 0-48 h after epidural blood patch. All others were considered partial success. Multinominal logistic regression was used for statistical analyses with $P<0.01$ considered statistically significant.

Results

In all, 643 women received an epidural blood patch. Complete data to classify failure were available in 591 (91.9%) women. Failed epidural blood patch occurred in 167 (28.3%) patients; 195 (33.0%) were completely successful and 229 (38.7%) partially successful. A total of 126 women (19.8%) received a second epidural blood patch. A statistically significant association with failure was observed in patients with a history of migraine, when the accidental dural puncture occurred between lumbar levels L1/L3 compared with L3/L5 and when epidural blood patch was performed <48 h compared with ≥48 h after accidental dural puncture. In patients having radiological investigations, three intracranial bleeds were diagnosed.

Conclusions

Failed epidural blood patch occurred in 28.3% of women. Independent modifiable factors associated with failure were higher lumbar level of accidental dural puncture and short interval between accidental dural puncture and epidural blood patch. A history of migraine was associated with a higher risk of second epidural blood patch.

INTRODUCTION

Accidental dural puncture (ADP), whilst performing epidural labour analgesia, occurs in 0.5-1.5% of procedures.[1,2] This iatrogenic injury causes leakage of CSF and can result in an intense post-dural puncture headache (PDPH), which is commonly postural.[3] PDPH often results in the patient being bedridden, thus delaying maternal recovery and mother-child bonding.[4,5] Several treatment options exist for the management of PDPH, but an epidural blood patch (EBP), where autologous blood is injected into the epidural space near the ADP site, is usually considered to be the best therapeutic option, although up to 30% of patients require a second EBP because of recurrent symptoms.[6-9] An EBP is believed to have a two-fold effect: immediate restoration of the reduced intracranial CSF pressure and a secondary effect resulting from clot formation and reparation of the dural tear.[10] Although EBP is an invasive procedure, serious complications have rarely been described.[7,11]

The European Practices in the Management of Accidental Dural Puncture in Obstetrics (EPiMAP) was an international cohort study that described current practices in the management of PDPH and studied risk factors of failure of EBP. In the first part of the study, we identified factors associated with the preference for use of EBP or conservative management after diagnosis of PDPH.[12] The main objective of the present study was to determine factors associated with failure of EBP. Some of these factors have been described previously, such as injection of lower volumes of blood during EBP and early application of EBP after ADP.[8,9,13,14] However, a causal relationship between timing of EBP and failure has not been proven. It has been suggested that an attempt to inject up to 20 ml of autologous blood should be made, as higher volumes have not been shown to improve success rates even when height adjusted.[7-9,15] An association between risk of intracranial bleeding and delay in application of EBP has been suggested, but early application of EBP may be associated with failure.[13,16] The primary aim of the present EPiMAP study was to determine risk factors associated with failure of the first EBP in women having PDPH after obstetric neuraxial anaesthesia and analgesia.

METHODS

This was a prospective, multicentre cohort study. Data were collected from January 1, 2016, to December 31, 2018, with a follow-up period of 3 months ending March 31, 2019. The study was registered on ClinicalTrials.gov (NCT02362828), and ethical committee approval was obtained in each participating country, either locally or nationally, depending on country requirements. Signed informed consent was obtained from each patient before inclusion when requested by the local/national ethics committee. Inclusion and exclusion criteria were the same as those described in EPiMAP I except only women who received an EBP were included in the present study.[12]

Post-dural puncture headache was diagnosed by a board-certified anaesthesiologist according to the prevailing International Classification of Headache Disorders (ICHD-II 2d). [17] The ICHD-II describes PDPH as a headache that worsens within 15 min in the upright position and improves within 15 min after lying down, which develops within 5 days after suspected or confirmed dural puncture, and which may or may not be accompanied by neck stiffness and vestibular, visual, or auditory symptoms.[17] Headache intensity was measured in the upright (sitting/standing) and supine (lying) positions using a numeric rating scale (NRS), with 0=no pain and 10=worst imaginable pain, and classified as none (NRS=0), mild (1-3), moderate (4-6), and severe (7-10) in the upright position.

The need for an EBP was ascertained by a certified anaesthesiologist immediately before its application, depending on headache intensity during the previous 6-12 h, accompanying symptoms and local traditions and guidelines in each centre/country. The timing of the EBP, the position of the patient, the lumbar level chosen for the EBP, the volume of blood injected, the duration of bed rest, the timing of home discharge, and the need for a second or third EBP were at the discretion of the anaesthesiologist. CT, MRI, or Doppler ultrasonography was used when needed to exclude other pathological processes, in accordance with existing clinical practice. An open-source clinical data management system (OpenClinica™), was used by the European Society of Anaesthesiology and Intensive Care (ESAIC), to collect data in accordance with the general data protection regulations. Patients were followed up during hospital stay, by telephone after discharge, and after 7 days and 3 months by a standardised telephone interview.

The primary outcome was failed EBP, defined as a headache intensity with NRS ≥7 in the upright position at 4, 24, and or 48 h after application of EBP or the need for a second EBP. A complete success was defined as no headache (NRS=0) at 4, 24, and 48 h after EBP in the upright position and no subsequent EBP application, and partial success included all other patients not categorized as success or failure. If the patient had no headache at 4 or 24 h and was discharged before 48 h and not readmitted with headache, the EBP was also considered a complete success. The terms chronic headache, vertebral column pathology, and technical difficulty in insertion of epidural were not defined *pre hoc* but left to the discretion of the attending anaesthesiologist.

ESAIC was the sponsor and coordinated the study, ensuring quality assurance and control systems using standard operating procedures. Data were generated, documented, and reported in compliance with the protocol Good Clinical Practice, and the local regulatory requirements. The sponsor ensured agreement from all involved parties and access to all trial-related sites, source data/documents, reports for monitoring and auditing, and inspection by domestic and foreign regulatory authorities. The local principal investigator verified data quality and registration and was controlled by the sponsor with random assessments of centres to confirm correctness of data.

Table 1. Characteristics of study population.

Epidural blood patch group (n=643)	n (%)
Patient characteristics	
Mother's age (yr), median (IQR; min-max)	31 (28-34; 18-46)
BMI (kg/m^2), median (IQR) (n=642)	26.7 (24.0-30.1)
<25 normal (+underweight*)	219 (34.1)
25.0-29.9 (pre-obesity)	251 (39.1)
≥30.0 (obesity)†	172 (26.8)
Previous history of	
PDPH headache	17 (2.6)
Chronic headache	30 (4.7)
Migraine	98 (15.2)
Vertebral column pathology	49 (7.6)
University as highest education (n=641)	308 (48.0)
Mode of delivery	
Spontaneous	452 (70.3)
Instrumental	79 (12.3)
Caesarean delivery	112 (17.4)
Characteristics of epidural insertion	
Needle size at accidental dural puncture	
18-20G	518 (80.6)
16-17G	125 (19.4)
Method for detecting loss of resistance (n=642)	
Saline	560 (87.2)
Air	71 (11.1)
Both	11 (1.7)
Position of patient at accidental dural puncture (n=640)	
Sitting	519 (81.1)
Lying	121 (18.9)
Level of accidental dural puncture (n=642)	
L3/L5	421 (65.6)
L1/L3	221 (34.4)
Multiple attempts at different levels	304 (47.3)
Intrathecal catheter placed after accidental dural puncture	91 (14.2)

Experience of operator providing epidural analgesia (yr)	
≥1	502 (78.1)
<1	141 (21.9)
How accidental dural puncture was determined	
CSF in epidural needle	321 (49.9)
CSF in catheter or positive aspiration test or positive intrathecal test dose, without CSF in needle	85 (13.2)
Only classical signs of PDPH postpartum	237 (36.9)
Second accidental dural puncture occurring when new epidural needle was inserted (n=641)	
No	429 (66.9)
Yes	64 (10.0)
Not applicable	148 (23.1)
Time for first symptoms of PDPH after accidental dural puncture (h) (n=639), median (IQR; min-max)	16 (8-28; 0-120)
Symptoms other than classical PDPH, before/after confirmed PDPH	
Nausea/vomiting	178 (27.7)
Auditory symptoms	172 (26.7)
Diplopia	18 (2.8)
Dizziness	181 (28.1)
Other visual symptoms	106 (16.5)
Tinnitus	90 (14.0)
Neck	69 (10.7)
Others	66 (10.3)
Characteristics of EBP management	
Hours from ADP to EBP, median (IQR; min-max)‡	68 (47-97; 0.5-270)
Patient initially refused EBP	13 (2.0)
Experience of the operator in performing EBP (yr), n	
0	52 (8.1)
1-10	224 (34.8)
>10	367 (57.1)
Position of patient during EBP	
Sitting	344 (53.5)
Lying	299 (46.5)
Worst pain intensity upright 6-12 h before EBP (NRS), median (IQR; min-max) (n=630)	9 (8-10; 0-10)

Orthostatic headache classified 6-12 h before EBP¶ (n=630)	555 (88.1)
Level of insertion of EBP (n=642)	
L3/L5	444 (69.2)
L1/L3	198 (30.8)
Technical difficulties in performing EBP	60 (9.3)
Volume of blood injected during EBP (ml), median (IQR; min-max)	20 (18-20, 8-40)
First mobilisation after EBP (h) (n=640), median (IQR; min-max)	2 (2-4; 0-24)
Country	
Spain	110 (17.1)
France	84 (13.1)
Sweden	84 (13.1)
Portugal	57 (8.9)
Germany	56 (8.7)
Netherlands	46 (7.2)
Belgium	42 (6.5)
Israel	25 (3.9)
Finland	22 (3.4)
Norway	22 (3.4)
Switzerland	22 (3.4)
Other	73 (11.3)

Data presented as n (%) unless otherwise stated.
Abbreviations: ADP, accidental dural puncture; BMI, body mass index; CSF, cerebrospinal fluid; EBP, epidural blood patch; IQR, interquartile range; NRS, numeric rating score; PDPH, post-dural puncture headache.
** Includes underweight (six patients)*
† BMI ≥35 kg/m² (45 patients)
‡ <24 h between epidural needle insertion and EBP (25 patients)
¶ Orthostatic headache was classified as delta pain intensity ≥2 NRS higher upright than lying 6-12 h before EBP

Statistical analysis

Because of the limited number of randomised studies to estimate potential risk factors for EBP failure, we used low volume of blood injected into the epidural space during EBP as one potential risk factor for failure to determine sample size. An absolute reduction of failure rates from 39% to 27% was found by Paech and colleagues[9] when comparing women who were allocated to receive 15 ml vs 20 ml of blood during EBP. Using these data, we estimated that 636 patients receiving an EBP would be needed for 90% statistical power when using a 5%

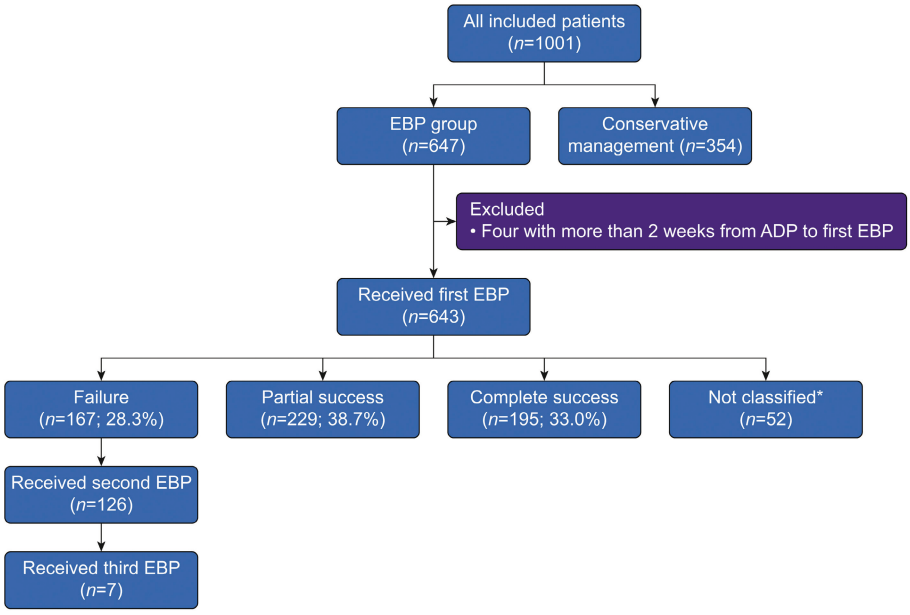
significance level. Multinominal logistic regression was used with the outcome categorized as EBP resulting in a complete success (the reference), partial success, or failure.

Independent variables identified *a priori* as potential causes of failure from the literature included intensity of headache before EBP, experience of the anaesthesiologist performing the EBP, epidural needle size, position of the patient during EBP, volume of blood injected, time from ADP to EBP, and duration of rest before mobilisation after EBP. Other variables listed in Table 1 were included as potential risk factors after discussion within the steering committee and before data analyses. The unadjusted models were adjusted for country of residence, with countries including fewer than 15 patients collapsed into one category. The adjusted model was estimated with all variables in the model to evaluate each variable's independent association with the outcome.

Continuous variables were categorised in tertiles, with some exceptions. Hours from ADP to EBP were categorised <48, 48 to <72 h, and ≥72 h. Body mass index (BMI) was categorised as BMI <25, 25-29.9, or ≥30 kg/m^2.[18] Needle size used during ADP was characterised as large (16G or 17G) or small (18G, 19G, or 20G) bore; vertebral interspace during ADP and at EBP insertion as high (L1/L3; L1-L2 or L2-L3 interspace) or low (L3/L5; L3-L4 or L4-L5 interspace); and mobilisation time after EBP as early (<2 h), intermediate (2-4 h), or late (>4 h). Experience of the anaesthesia operator during ADP was categorised as experience <1 or ≥1 yr. Orthostatic headache was defined as NRS pain intensity in the upright position-supine position ≥2.

Regression diagnostics and sensitivity analysis were performed by excluding outliers, and influential subjects were identified using Pearson residuals, deviance residuals, and Pregibon leverage statistics, but there were no different findings. We evaluated the potential collinearity issues by estimating the variance inflation factor (VIF); the variables showed a VIF score between 1 and 2, much lower than 10, which is a rule of thumb for collinearity. Because of missing data on some independent variables and outcomes, multiple imputation was performed using logistic and multinominal regression with chained equations based on the concept of Rubin.[19] All variables in the adjusted model and the outcome were used as independent variables for the imputation, which was repeated 10 times. Variables showing statistical significance in the adjusted model were further evaluated by comparing the NRS pain intensity at different time points pre-EBP and post-EBP with Kruskal-Wallis and Mann-Whitney tests, and by comparing the frequency of second EBP with χ^2 or Fisher's exact test when appropriate and differences in orthostatic headache with χ^2 test. Multinominal logistic regression gives odds ratios (ORs) with 95% confidence intervals (CIs) as association measures. To reduce the risk of false-positive findings because many independent variables were hypothesised as risk factors, a P-value <0.01 was set as statistically significant. All statistical calculations were done in Stata release 14 (StataCorp, College Station, TX, USA).

Fig 1. Strengthening the Reporting of Observational Studies in Epidemiology diagram for inclusion or exclusion of patients.



Please see text for definitions of failure, partial success, and complete success.
Abbreviations: ADP, accidental dural puncture; EBP, epidural blood patch.
**Primary outcome not classified in 52 patients because of missing pain intensity data.*

RESULTS

From a total of 1001 patients with PDPH who were included in the EPiMAP database, 647 patients from 24 countries and 125 centres received an EBP (64.6%).[12] Of these, four patients receiving an EBP >2 weeks after ADP were excluded from the present analysis, and a total of 643 women from 24 countries were included in the final analyses (Fig 1). The number of patients included and the rates of failures, partial success, and complete success varied considerably in different countries (Supplementary Fig.1S). Patient characteristics with missing data on some variables are shown in Table 1.

Headache intensities before and after application of EBP are shown in Table 2, and the numbers (%) of completely successful, partially successful, and failed EBP are shown in Fig 1. A total of 52 of 643 (8.1%) patients could not be classified for the primary outcome because of some missing pain intensity data. In all, failure of first EBP was seen in 167 of 591 (28.3%; 95% CI: 24.6-32.1%) patients, partial success in 229 of 591 (38.7%; 95% CI: 34.8-42.8%), and 195 (33.0%; 95% CI: 29.2-36.9%) of EBP were completely successful. Severe headache was

reported by an increasing proportion of women between 4 and 24 h after EBP (Table 2), and a second EBP was performed in 126/643 women (19.6%; 95% CI: 16.6-22.9%).

Table 2. Analgesia outcomes. EBP group, n=643.

Pain intensity in the upright position	n	None (NRS 0).	Mild (NRS 1-3).	Moderate (NRS 4-6).	Severe (NRS 7-10).
		n (%)	n (%)	n (%)	n (%)
6-12 h before EBP	630	1 (0.2)	3 (0.5)	74 (11.7)	552 (87.6)
After EBP	641	250 (39.0)	249 (38.9)	97 (15.1)	45 (7.0)
4 h after EBP	575	276 (48.0)	207 (36.0)	71 (12.4)	21 (3.6)
24 h after EBP	636	344 (54.1)	167 (26.3)	60 (9.4)	65 (10.2)
48 h after EBP (only readmitted or patients with persistent PDPH measured at 48 h)	199	7 (3.5)	18 (9.1)	54 (27.1)	120 (60.3)
Having a second EBP		19.6% (126 of 643)			
Hours from first to second EBP, median (IQR)	126	49 (44-69)			
Second EBP within 24 h		6.4% (8 of 126)			
Second EBP within 48 h		41.3% (52 of 126)			

Abbreviations: EBP, epidural blood patch; IQR, inter-quartile range; NRS, numeric rating score; PDPH, postdural puncture headache.

In the multinominal adjusted logistic regression model with multiple imputation, the following variables were statistically significantly associated with a greater risk of failure of the EBP (P<0.01): history of migraine compared with no history of migraine, and ADP occurring at a higher level (L1/L3) compared with a lower level (L3/L5) (Table 3). EBP volume was not found to be associated with failure. All variables included in the model are presented in Supplementary table 1S. Complementary analysis did not show any different association when combining the level of ADP with EBP (Supplementary table 2S). The adjusted failure risk of an EBP was lowest when ADP had occurred at L4-L5, higher with an ADP at L3-L4, and highest if ADP occurred at L2-L3 or L1-L2 levels (Supplementary table 3S). A significantly lower risk of failure of the EBP was observed when there was a longer time interval between ADP and EBP: EBP ≥48 to <72 h after ADP and EBP ≥72 h after ADP compared with EBP <48 h (Table 3). Higher levels (L1/L3) were associated with greater risk of partial success compared with lower levels (L3/L5). EBP ≥72 h after ADP was associated with a significant lower risk of partial success (Table 3). The same variables associated with a significant risk of EBP failure were also found in a complete case analysis, not using multiple imputation for missing data.

Table 3. Significant variables from the adjusted multinominal logistic regression with outcome classified as complete success (reference), partial success, or failure.

	Partial success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Previous history of migraine headache								
No	Reference		Reference		Reference		Reference	
Yes	1.06 (0.57-1.95)	0.86	1.25 (0.61-2.56)	0.55	2.09 (1.16-3.78)	0.0149	3.16 (1.48-6.78)	0.0032
Level of accidental dural puncture								
L3/L5	Reference		Reference		Reference		Reference	
L1/L3	1.83 (1.12-2.98)	0.0152	2.69 (1.47-4.94)	0.0014	2.11 (1.23-3.60)	0.0065	3.28 (1.64-6.53)	0.0008
Time from accidental dural puncture to epidural blood patch (h)								
<48	Reference		Reference		Reference		Reference	
48 to <72	0.70 (0.38-1.28)	0.24	0.60 (0.30-1.19)	0.14	0.43 (0.23-0.78)	0.006	0.37 (0.18-0.77)	0.0073
≥72	0.45 (0.25-0.78)	0.0046	0.36 (0.19-0.70)	0.0022	0.10 (0.06-0.19)	<0.0001	0.08 (0.04-0.16)	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio.

**The unadjusted analysis was adjusted for country, and multiple imputation is used for missing data on variables and outcome; n=643.*

†The adjusted analysis was adjusted for all variables in Supplementary table 1S, and multiple imputation is used for missing data on variables and outcome; n=643.

For all variables associated with significant risk of EBP failure, headache intensities in the upright position before and after application of EBP and the frequency of a second EBP are presented in Supplementary table 4S. A higher level of ADP (L1/L3) compared with lower (L3/L5) was associated with greater headache intensity in the first 24 h after EBP (P<0.01) but not associated with an increased risk of higher NRS scores at 48 h, or receiving a second EBP, whilst a history of migraine was only significantly associated with a greater risk of receiving a second EBP but not with an increased intensity of headache at any time after EBP. To differentiate migraine from PDPH, the incidence of orthostatic headache before and after application of EBP was compared between patients with or without migraine, but no differences were found (Supplementary table 5S). Finally, late application of EBP (≥72 h) was significantly associated with lower headache intensity at 4 and 24 h after EBP and with a lower risk of receiving a second EBP.

Of the 643 patients included in this study, 39 (6.1%; 95% CI: 4.3-8.2%) were further investigated using CT/MRI when symptoms did not resolve or changed in character after EBP. In three patients (0.5%; 95% CI: 0.1-1.4%), intracranial bleeding was found: two subdural and one subarachnoid haematoma. In all three patients, symptoms had resolved at 3 months without surgical intervention.

DISCUSSION

In this prospective, multicentre, international observational study, 28.3% of EBPs failed to relieve PDPH, 38.7% succeeded partially, and in 33.0% of patients EBP led to complete resolution. There was a significantly greater association with failure of EBP in patients with a history of migraine headache, who received a second EBP more frequently. When initial ADP occurred at higher lumbar segmental levels (L1/L3), there was a greater headache intensity in the first 24 h after EBP and an increased association for application of a second EBP. Regarding the EBP procedure itself, we found a higher success rate when the EBP was placed later (≥72 h) after ADP.

Post-dural puncture headache after ADP in parturients often results in severe, commonly orthostatic headache. If treated conservatively, PDPH is self-limiting in most patients, but when symptoms are severe, disabling, or persisting, physicians and patients often prefer treatment with an EBP.[12] Although EBP is an invasive procedure, it is rarely associated with major complications.[7] It usually relieves symptoms initially, but it may sometimes fail later in partially or completely eliminating the headache.[9,13,15] A satisfactory definition of failure or success of EBP has never been established, and failure has often been categorised as complete or partial.[8,9,14,20,21] Using our definition, the frequency of failure and the incidence of second EBP were similar to that reported in previous studies, including one that prospectively randomised patients to different volumes of blood administered for EBP.[9]

We identified several factors associated with EBP failure. Our finding of an association between history of migraine and failure of EBP is interesting. We found no statistically significant difference in the intensity of postural headache at any time after EBP between patients with and without migraine, and yet migraine patients received a second EBP significantly more often (31.6% vs 17.4%). A possible explanation for this might be that migraine headache was misdiagnosed as PDPH after EBP, as migraine is known to reappear in the first postpartum week.[22-24] However, this is unlikely for several reasons. In contrast to PDPH, migraine usually presents with unilateral headache, and postural changes have never been described.[25] Additionally, the incidence of orthostatic headache before and up to 24 h after EBP was similar between patients with and without migraine. However, this does not explain why, despite similar NRS scores after EBP, patients with migraine received a second EBP more frequently. Stress, anxiety, and pain around childbirth affect patients with a chronic pain syndrome, such as migraine, more often, resulting in differences in pain perception and pain catastrophising, which might explain a more frequent use of a second EBP,[26-28] which needs to be further investigated.

We also found a significantly increased incidence of failed EBP when the initial ADP occurred at a higher lumbar level (L1/L3) compared with lower levels (L3/L5). Although anaesthesiologists are unreliable in estimating the correct intervertebral space, this finding is interesting and not reported previously.[29]

Misclassification of the level of ADP (higher vs lower lumbar levels) by anaesthesiologists can occur, but no association with failure of EBP should be expected, as no underlying mechanisms are known that can explain an association between lumbar level of the initial ADP and subsequent therapy failure. Anatomical and physiological differences in meningeal neural innervation are known to exist between higher and lower spinal levels but are not likely to explain our findings.[30,31] The greater failure rate of an EBP when ADP occurs at L1/L3 compared with L3/L5 levels might depend on the level of the subsequent EBP. It is believed that blood injected during EBP migrates predominantly cephalad, and therefore, an EBP would be more successful if inserted at the same or lower lumbar level than where the ADP occurred.[7,32,33] However, we did not find that the level at which EBP was performed changed the association with failure at any lumbar level of ADP, nor was EBP level alone statistically significantly associated with failure. Therefore, the greater failure rate is more likely because of the higher level of initial ADP and not the level of subsequent EBP. Future research on PDPH and EBP should include the use of ultrasound to identify the lumbar level of neuraxial procedures to confirm these interesting findings.

Regarding timing of EBP application, we found that early application of EBP increased the association with failure, which confirmed findings of several smaller observational studies.[9,13,34] An overwhelming majority of patients had no or only mild headache immediately after inserting the EBP (77.9%) or 4 h later (84.0%). Nevertheless, headache intensity increased after 4 h, and almost one in five patients required a second EBP. It is possible that when

EBP is applied early after PDPH, the blood injected mixes freely with a large volume of CSF, leaking into the epidural space leading to poor clot formation, which might prevent sealing of the dural puncture, and subsequent failure of the EBP, as was shown in an in vitro study using thromboelastography.[30,35] These findings imply that increasing blood volume when EBP is applied early might improve success rates, but this has never been shown in clinical studies and needs to be investigated in future studies.[9,35]

We did not find an association between the volume of blood injected and EBP failure. However, most patients received ≥20 ml of blood, which was a common practice at the time this study was performed.[9] Although early application of EBP was associated with increased incidence of failure, it may nevertheless be desirable to perform early EBP because of severe intensity of the headache, or to avoid a potential risk of intracranial bleeding if applied late.[16,36] The latter was found in a recent retrospective observational cohort study using hospital readmission data.[16]

STUDY LIMITATIONS

As this is an observational study, no causation, only associations, could be determined for failure of EBP, and randomised studies are needed to confirm our findings for modifiable factors. The number of patients was limited compared to the number of variables included in the regression model. Low statistical power is a limitation, as several associations showed OR with low precision and wide 95% CI. We did not study all risk factors that might be associated with EBP failure, such as total analgesic consumption and fluid management before EBP. Most variables were identified *pre hoc* from observational studies, but some were included later, after a consensus within the Steering Committee.

As in previous studies, classification of EBP failure is not standardised, and distinguishing PDPH from migraine and other postpartum headaches can sometimes be difficult. Therefore, standardised definitions for failure should be developed. The study population did not include consecutive cases and was dependent on identification of PDPH by the midwife or attending physician in the maternity ward, and some cases may have been misdiagnosed or missed. However, our study comprises the largest number of patients with PDPH receiving an EBP collected prospectively in the obstetric population.

Another limitation of our study is that application of EBP (both first and second) and the timing of application were decisions made without objective criteria by the attending anaesthesiologist together with the patient and may have been arbitrary in some cases or dependent on local guidelines and traditions. Finally, body weight was registered differently by collaborators; some used pre-pregnancy weight and others weight immediately before delivery.

CONCLUSIONS

In this international, prospective, observational cohort study, we found that failure of epidural blood patch was seen in 28.3% of patients with post-dural puncture headache, with the rest either partially or completely successful. A history of migraine and a higher lumbar level of the accidental dural puncture were associated with a greater risk of failure of epidural blood patch. A lower incidence of epidural blood patch failure was seen when the epidural blood patch was performed ≥48 h after accidental dural puncture.

SUPPLEMENTARY DATA

Fig. 1S. Number of patients included and EBP treatment outcomes by country.

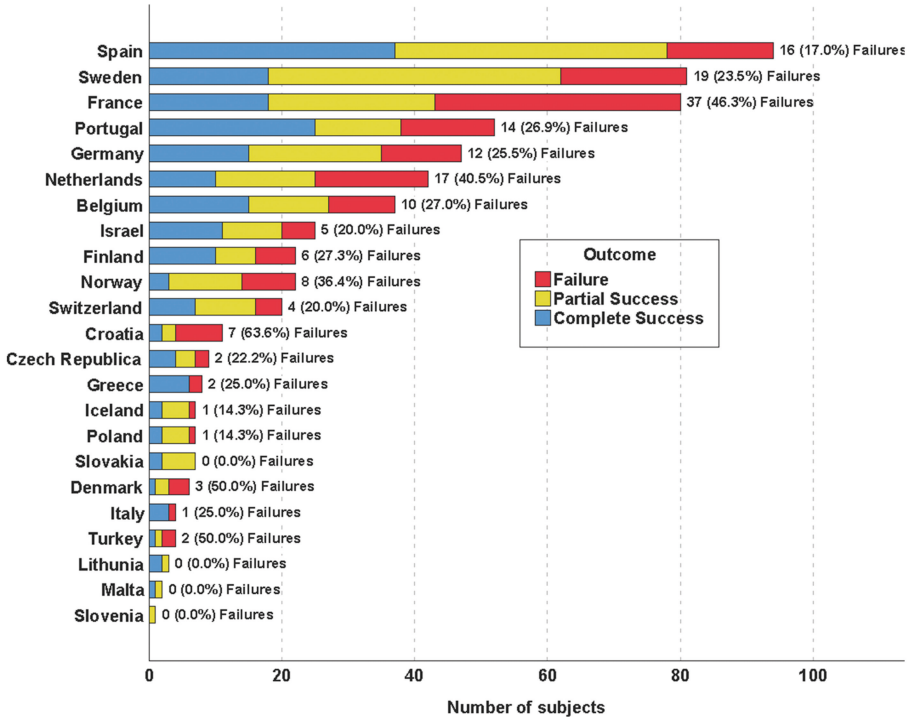


Table 1S. Multinominal logistic regression with outcome classified as complete success (reference), partial success and failure.

	Partial Success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Mother's age (years)								
18 - 29	Ref		Ref		Ref		Ref	
30 - 33	0.84 (0.52-1.37)	0.5	0.89 (0.51-1.57)	0.7	0.97 (0.59-1.60)	0.91	1.39 (0.74-2.62)	0.31
34 -- 46	0.94 (0.56-1.58)	0.82	0.90 (0.49-1.65)	0.74	0.87 (0.50-1.51)	0.61	1.05 (0.54-2.05)	0.89
Body-Mass Index (BMI) (kg/m^2)								
< 25 Normal (+underweight‡)	Ref		Ref		Ref		Ref	
25.0 - 29.9 Pre-obesity	0.72 (0.45-1.14)	0.16	0.70 (0.42-1.19)	0.19	0.72 (0.44-1.16)	0.18	0.78 (0.43-1.41)	0.41
≥ 30.0 Obesity	0.89 (0.53-1.49)	0.66	0.82 (0.45-1.49)	0.51	0.63 (0.36-1.11)	0.11	0.50 (0.24-1.03)	0.06
Previous history of								
PDPH headache	0.67 (0.17-2.65)	0.57	0.59 (0.12-2.82)	0.51	1.24 (0.36-4.31)	0.73	0.90 (0.20-4.10)	0.9
Chronic headache	2.49 (0.76-8.16)	0.13	2.63 (0.71-9.72)	0.15	2.68 (0.82-8.68)	0.1	1.89 (0.47-7.58)	0.37
Migraine	1.06 (0.57-1.95)	0.86	1.25 (0.61-2.56)	0.55	2.09 (1.16-3.78)	0.0149	3.16 (1.48-6.78)	0.0032
Vertebral column pathology	0.98 (0.46-2.07)	0.95	0.85 (0.36-2.03)	0.72	1.29 (0.60-2.75)	0.51	1.00 (0.39-2.58)	>0.99
University as highest education	1.05 (0.69-1.60)	0.8	1.00 (0.60-1.65)	0.99	0.78 (0.50-1.24)	0.3	0.67 (0.37-1.21)	0.18
Mode of delivery								
Spontaneous	Ref		Ref		Ref		Ref	
Instrumental	1.33 (0.71-2.47)	0.37	1.62 (0.80-3.29)	0.18	1.13 (0.57-2.24)	0.72	1.59 (0.69-3.68)	0.28
Cesarean section	1.02 (0.60-1.74)	0.94	0.86 (0.45-1.65)	0.65	0.84 (0.46-1.55)	0.58	1.17 (0.53-2.58)	0.7
Needle size at ADP								

18 - 20G	Ref		Ref		Ref		Ref	
16 - 17G	1.37 (0.67-2.79)	0.39	1.38 (0.61-3.12)	0.44	2.18 (1.07-4.43)	0.03	2.52 (1.03-6.13)	0.04
Method for detecting loss of resistance								
Saline[¶]	Ref		Ref		Ref		Ref	
Air	1.36 (0.71-2.64)	0.35	1.20 (0.56-2.56)	0.64	0.85 (0.38-1.89)	0.69	0.85 (0.30-2.38)	0.75
Position of patient at ADP								
Sitting	Ref		Ref		Ref		Ref	
Lying	0.68 (0.36-1.30)	0.25	0.54 (0.25-1.15)	0.11	0.88 (0.43-1.83)	0.74	0.51 (0.20-1.32)	0.17
Level of ADP								
L3/L5	Ref		Ref		Ref		Ref	
L1/L3	1.83 (1.12-2.98)	0.0152	2.69 (1.47-4.94)	0.0014	2.11 (1.23-3.60)	0.0065	3.28 (1.64-6.53)	0.0008
Multiple attempts at different levels	1.15 (0.77-1.71)	0.51	1.13 (0.71-1.79)	0.61	1.16 (0.75-1.78)	0.5	0.87 (0.50-1.48)	0.6
Intrathecal catheter placed after ADP	1.18 (0.65-2.14)	0.59	1.17 (0.54-2.51)	0.69	1.27 (0.69-2.36)	0.44	1.55 (0.65-3.69)	0.32
Experience of operator providing epidural analgesia (EDA)								
≥ 1 yr	Ref		Ref		Ref		Ref	
< 1 yr	0.76 (0.46-1.25)	0.28	0.79 (0.44-1.42)	0.43	0.43 (0.23-0.80)	0.0082	0.39 (0.19-0.82)	0.0131
How was ADP determined								
CSF in epidural needle	Ref		Ref		Ref		Ref	

Table 1S. Continued.

	Partial Success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	**P-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
CSF in catheter or positive aspiration test or spinal anesthesia after test dose. without CSF in needle	0.71 (0.39-1.30)	0.27	0.62 (0.31-1.23)	0.17	0.79 (0.40-1.57)	0.51	0.75 (0.31-1.83)	0.53
Only classical signs of PDPH postpartum	0.73 (0.47-1.12)	0.15	0.80 (0.46-1.40)	0.44	0.93 (0.59-1.47)	0.75	1.49 (0.78-2.82)	0.22
Second ADP occurring when new epidural needle was inserted								
No	Ref		Ref		Ref		Ref	
Yes	2.84 (1.32-6.12)	0.0078	2.82 (1.21-6.57)	0.016	2.12 (0.95-4.72)	0.07	2.18 (0.86-5.53)	0.1
Not applicable	1.41 (0.88-2.28)	0.15	1.51 (0.84-2.72)	0.16	1.15 (0.69-1.93)	0.59	0.81 (0.41-1.62)	0.56
Time for first symptoms of PDPH after ADP (hours)								
0-10hr	Ref		Ref		Ref		Ref	
11-24hr	1.30 (0.80-2.13)	0.29	1.44 (0.82-2.55)	0.2	1.10 (0.67-1.80)	0.72	1.19 (0.64-2.22)	0.58
25-120hr	1.01 (0.63-1.63)	0.96	1.33 (0.75-2.36)	0.33	0.36 (0.20-0.64)	0.0005	0.65 (0.31-1.35)	0.25
Hours from ADP to EBP								
< 48hr	Ref		Ref		Ref		Ref	
48 to <72hr	0.70 (0.38-1.28)	0.24	0.60 (0.30-1.19)	0.14	0.43 (0.23-0.78)	0.006	0.37 (0.18-0.77)	0.0073
≥72hr	0.45 (0.25-0.78)	0.0046	0.36 (0.19-0.70)	0.0022	0.10 (0.06-0.19)	<0.0001	0.08 (0.04-0.16)	<0.0001

Experience of the operator in performing EBP (n)								
< 1	1.28 (0.55-2.98)	0.57	1.10 (0.43-2.79)	0.85	1.57 (0.68-3.59)	0.29	1.30 (0.48-3.48)	0.6
1-10	1.60 (1.01-2.55)	0.04	1.69 (0.99-2.90)	0.06	1.53 (0.94-2.48)	0.09	1.10 (0.61-2.00)	0.75
> 10	Ref		Ref		Ref		Ref	
Position of patient during EBP								
Sitting	Ref		Ref		Ref		Ref	
Lying	0.67 (0.41-1.10)	0.11	0.59 (0.33-1.06)	0.08	0.67 (0.39-1.46)	0.14	0.62 (0.31-1.23)	0.17
Worst pain intensity upright 6-12hr before EBP (NRS)								
NRS ≤ 8	Ref		Ref		Ref		Ref	
NRS 9	1.14 (0.67-1.92)	0.63	1.15 (0.64-2.06)	0.65	1.44 (0.81-2.56)	0.22	1.61 (0.81-3.21)	0.18
NRS 10	0.72 (0.45-1.14)	0.16	0.62 (0.36-1.06)	0.08	1.67 (1.03-2.70)	0.04	1.41 (0.78-2.55)	0.26
Orthostatic headache classified 6-12hr before EBP#								
<2 NRS higher upright	Ref		Ref		Ref		Ref	
≥2 NRS higher upright	0.68 (0.37-1.24)	0.21	0.67 (0.34-1.31)	0.24	0.88 (0.44-1.78)	0.73	0.85 (0.36-1.96)	0.7
Level of insertion EBP								
L3/L5	Ref		Ref		Ref		Ref	
L1/L3	1.11 (0.69-1.77)	0.67	0.87 (0.49-1.53)	0.63	1.03 (0.62-1.72)	0.9	0.76 (0.39-1.49)	0.43
Technical difficulties in performing EBP								
No	Ref		Ref		Ref		Ref	

Table 1S. Continued.

	Partial Success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	**P-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Yes	2.17 (0.97-4.86)	0.06	2.14 (0.84-5.50)	0.11	2.46 (1.07-5.65)	0.03	3.52 (1.24-9.98)	0.0183
Volume of blood injected during EBP (ml)								
8-19 ml	1.22 (0.78-1.92)	0.37	1.19 (0.70-2.02)	0.51	1.48 (0.90-2.44)	0.12	1.60 (0.85-3.03)	0.15
20 ml	Ref		Ref		Ref		Ref	
21-40 ml	0.91 (0.50-1.66)	0.77	0.70 (0.35-1.41)	0.32	1.34 (0.70-2.56)	0.38	1.39 (0.61-3.15)	0.43
First mobilization after EBP (hours)								
< 2hr	1.45 (0.84-2.51)	0.18	1.86 (0.99-3.50)	0.05	0.93 (0.48-1.80)	0.82	0.86 (0.38-1.93)	0.72
2-4hr	Ref		Ref		Ref		Ref	
5-24hr	1.19 (0.63-2.24)	0.59	1.40 (0.68-2.88)	0.36	2.03 (1.04-3.96)	0.04	2.63 (1.13-6.09)	0.02
Symptoms other than classical PDPH. before/after confirmed PDPH								
Nausea/vomiting	0.65 (0.41-1.02)	0.06	0.66 (0.39-1.13)	0.13	0.91 (0.56-1.46)	0.69	0.81 (0.44-1.48)	0.49
Auditory symptoms	1.08 (0.70-1.68)	0.71	1.26 (0.74-2.14)	0.4	0.74 (0.45-1.22)	0.24	0.76 (0.40-1.42)	0.38
Diplopia	0.53 (0.14-2.03)	0.36	0.61 (0.14-2.66)	0.51	1.34 (0.40-4.44)	0.63	1.62 (0.37-7.10)	0.52
Dizziness	0.93 (0.58-1.47)	0.74	0.85 (0.51-1.43)	0.54	1.20 (0.75-1.94)	0.45	1.23 (0.69-2.21)	0.48
Other visual symptoms	0.97 (0.56-1.69)	0.92	0.97 (0.50-1.86)	0.93	1.27 (0.72-2.26)	0.41	1.17 (0.57-2.39)	0.66
Tinnitus	1.03 (0.58-1.81)	0.92	1.00 (0.50-2.00)	>0.99	0.95 (0.51-1.76)	0.87	1.50 (0.69-3.24)	0.31

Neck	0.88 (0.47-1.67)	0.71	1.10 (0.54-2.26)	0.79	0.88 (0.45-1.73)	0.71	1.06 (0.45-2.48)	0.89
Others	0.94 (0.49-1.82)	0.85	0.87 (0.42-1.83)	0.72	1.04 (0.51-2.12)	0.92	0.77 (0.33-1.82)	0.56
Country								
Spain	Ref		Ref		Ref		Ref	
France	1.33 (0.62-2.86)	0.46	1.07 (0.31-3.68)	0.91	4.81 (2.17-10.7)	<0.01	2.38 (0.60-9.44)	0.22
Sweden	2.33 (1.16-4.71)	0.02	2.85 (1.00-8.12)	0.04	2.43 (1.03-5.73)	0.04	4.13 (1.12-15.3)	0.03
Portugal	0.50 (0.23-1.12)	0.09	0.51 (0.20-1.30)	0.16	1.36 (0.58-3.21)	0.47	1.98 (0.66-5.99)	0.22
Germany	1.20 (0.50-2.87)	0.67	1.00 (0.36-2.74)	>0.99	1.73 (0.68-4.41)	0.25	1.12 (0.33-3.78)	0.85
Netherlands	1.31 (0.50-3.43)	0.58	0.59 (0.18-1.85)	0.36	3.98 (1.48-10.7)	<0.01	1.68 (0.45-6.29)	0.44
Belgium	0.82 (0.35-1.90)	0.65	0.99 (0.35-2.78)	0.99	1.65 (0.61-4.44)	0.32	1.91 (0.55-6.66)	0.31
Israel	0.76 (0.28-2.05)	0.59	1.28 (0.35-4.67)	0.71	1.06 (0.32-3.53)	0.93	1.90 (0.36-10.1)	0.45
Finland	0.56 (0.18-1.69)	0.3	0.34 (0.07-1.57)	0.17	1.40 (0.44-4.48)	0.57	0.98 (0.16-6.06)	0.98
Norway	3.42 (0.89-13.2)	0.07	2.47 (0.51-11.9)	0.26	6.22 (1.46-26.4)	0.01	6.14 (1.04-36.2)	0.04
Switzerland	1.12 (0.38-3.32)	0.83	1.94 (0.52-7.22)	0.32	1.28 (0.31-5.26)	0.73	1.49 (0.26-8.44)	0.65
Other	0.84 (0.41-1.74)	0.65	0.79 (0.30-2.09)	0.64	1.72 (0.75-3.93)	0.2	1.30 (0.41-4.10)	0.66

Multiple imputation (MI) is used for missing data on variables and outcome, n=643

Abbreviations: NRS, numeric rating score; EBP, epidural blood patch, BMI, body mass index; PDPH, post-dural puncture headache; ADP, accidental dural puncture.

** The unadjusted analysis was adjusted for country.*

† The adjusted analysis was adjusted for all variables in the table.

‡ Includes: underweight (6 patients).

¶ Includes 11 patients with both saline and air.

 # Orthostatic headache was classified as delta pain intensity ≥2 NRS higher upright than lying 6-12hr before EBP.

Table 2S. Relationship between level of ADP and EBP in multinominal logistic regression with outcome classified as complete success (reference), partial success and failure.

Level of ADP	Level of EBP	Partial Success				Failure			
		Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
L3/L5	L3/L5	Reference		Reference		Reference		Reference	
L1/L3	L3/L5	2.19 (1.10-4.37)	0.03	2.78 (1.28-6.04)	0.0097	2.46 (1.20-5.04)	0.014	3.68 (1.55-8.70)	0.0031
L3/L5	L1/L3	1.09 (0.56-2.12)	0.8	0.89 (0.42-1.88)	0.76	0.88 (0.41-2.91)	0.8	0.89 (0.34-2.30)	0.81
L1/L3	L1/L3	1.66 (0.92-3.00)	0.09	2.31 (1.17-4.57)	0.016	1.78 (0.93-3.43)	0.09	2.42 (1.10-5.34)	0.03
Classified as L1 to L5									
Same level		Reference		Reference		Reference		Reference	
EBP lower than ADP		1.42 (0.87-2.31)	0.16	1.31 (0.77-2.22)	0.32	1.13 (0.69-1.87)	0.63	1.02 (0.57-1.83)	0.95
EBP higher than ADP		0.96 (0.57-1.63)	0.88	0.70 (0.38-1.27)	0.24	0.55 (0.29-1.03)	0.06	0.40 (0.18-0.85)	0.018

Multiple imputation (MI) is used for missing data on variables and outcome, n=643.

Abbreviations: ADP, accidental dural puncture; CI, confidence interval; EBP, epidural blood patch; OR, odds ratio.

** The unadjusted analysis was adjusted for country.*

† The adjusted analysis was adjusted for all variables in the table 1S

Table 3S. Complemented adjusted multinominal logistic regression with outcome classified as complete success (reference), partial success, and failure, and level of ADP in four categories.

Level of ADP	Partial Success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	P-value
L1 - L2	1.84 (0.65-5.18)	0.25	1.97 (0.60-6.45)	0.26	2.98 (1.05-8.50)	0.04	3.02 (0.83-11.0)	0.09
L2 - L3	1.76 (1.05-2.93)	0.03	2.63 (1.41-4.91)	0.0024	1.87 (1.06-3.29)	0.03	3.00 (1.47-6.12)	0.0026
L3 - L4	Ref		Ref		Ref		Ref	
L4 - L5	0.81 (0.45-1.44)	0.46	0.64 (0.33-1.26)	0.2	0.71 (0.38-1.35)	0.3	0.52 (0.24-1.14)	0.1

Abbreviations: ADP, accidental dural puncture; CI, confidence interval; OR, odds ratio.

** The unadjusted analysis was adjusted for country and multiple imputation is used for missing data on variables and outcome, n=643.*

† The adjusted analysis was adjusted for all variables in supplemental table 1S and multiple imputation is used for missing data on variables and outcome, n=643

Table 4S. NRS pain intensity upright before and after the first EBP and frequency of second EBP by the statistical significant variables (p<0.01) in adjusted regression model for failures in table 3.

	Level of ADP L1 / L3 (n=221)					Level of ADP L3 / L5 (n=421)	
Pain intensity		**None NRS = 0**	**Mild NRS 1-3**	**Moderate NRS 4-6**	**Severe NRS 7-10**		**None NRS = 0**
	n	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n**	**n (%)**
6-12hrs before EBP	218	0 (0.0)	0 (0.0)	21 (9.6)	197 (90.4)	411	1 (0.2)
After EBP	220	67 (30.4)	92 (41.8)	36 (16.4)	25 (11.4)	420	183 (43.6)
4hrs after EBP	204	75 (36.8)	80 (39.2)	38 (18.6)	11 (5.4)	370	201 (54.3)
24hrs after EBP	216	99 (45.8)	61 (28.2)	24 (11.1)	32 (14.8)	419	244 (58.2)
48hrs after EBP†	84	4 (4.8)	7 (8.3)	25 (29.8)	48 (57.1)	115	3 (2.6)
Having a second EBP	47	21.3% (47 of 221)				79	18.8% (79 of 421)
Hours from first to second EBP, median (IQR)		49 (45-64)					52 (43-72)
Second EBP within 24hrs		10.6% (5 of 47)					3.8% (3 of 79)
Second EBP within 48hrs		44.7% (21 of 47)					39.2% (31 of 79)

	Previous history of Migraine (n=98)					No previous history of Migraine (n=545)	
Pain intensity		**None NRS = 0**	**Mild NRS 1-3**	**Moderate NRS 4-6**	**Severe NRS 7-10**		**None NRS = 0**
	n	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n**	**n (%)**
6-12hrs before EBP	94	0 (0.0)	0 (0.0)	13 (13.8)	81 (86.2)	536	1 (0.2)
After EBP	98	44 (44.9)	32 (32.6)	16 (16.3)	6 (6.1)	543	206 (37.9)
4hrs after EBP	85	44 (51.8)	29 (34.1)	9 (10.6)	3 (3.5)	490	232 (47.4)
24hrs after EBP	97	50 (51.6)	21 (21.6)	15 (15.5)	11 (11.3)	539	294 (54.6)
48hrs after EBP†	35	1 (2.9)	3 (8.6)	11 (31.4)	20 (57.1)	164	6 (3.7)
Having a second EBP	31	31.6% (31 of 98)				95	17.4% (95 of 545)
Hours from first to second EBP, median (IQR)		49 (44-69)					50 (44-69)
Second EBP within 24hrs		6.4% (2 of 31)					6.3% (6 of 95)
Second EBP within 48hrs		45.2% (14 of 31)					40.0% (38 of 95)

	Hours from ADP to EBP <48 (n=164)					Hours from ADP to EBP 48-<72 (n=184)	
Pain intensity		**None NRS = 0**	**Mild NRS 1-3**	**Moderate NRS 4-6**	**Severe NRS 7-10**		**None NRS = 0**
	n	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n**	**n (%)**
6-12hrs before EBP	158	0 (0.0)	1 (0.6)	19 (12.0)	138 (87.3)	182	0 (0.0)
After EBP	162	51 (31.5)	68 (42.0)	37 (22.8)	6 (3.7)	183	69 (37.7)
4hrs after EBP	148	61 (41.2)	57 (38.5)	25 (16.9)	5 (3.4)	167	73 (43.7)
24hrs after EBP	163	76 (46.6)	42 (25.8)	21 (12.9)	24 (14.7)	183	87 (47.5)
48hrs after EBP†	86	2 (2.3)	7 (8.1)	18 (20.9)	59 (68.6)	69	4 (5.8)
Having a second EBP	62	37.8% (62 of 164)				43	23.4% (43 of 184)
Hours from first to second EBP, median (IQR)		51 (44-69)					50 (45-70)
Second EBP within 24hrs		6.4% (4 of 62)					2.3% (1 of 43)
Second EBP within 48hrs		40.3% (25 of 62)					37.2% (16 of 43)

Abbreviations: NRS, numeric rating score; EBP, epidural blood patch, ADP, accidental dural puncture; IQR, inter-quartile range.

** Mann-Whitney test for continuous and ordinal variables. χ^2 test or Fischer exact test when appropriate for binary variables.*

† Only patients re-admitted or with persistent PDPH were assessed at 48hrs.

‡ Kruskal-Wallis test for continuous and ordinal variables. χ^2 test or Fischer exact test when appropriate for binary variables.

¶ At 4hrs, the group ≥72h had significant lower pain intensity compared to the group <48hrs (P<0.01) and the group 48 to <72hrs (P<0.01). No significant differences in pain intensity between the groups <48hrs vs. 48 to <72hrs (P=0.80). Statistical method was Mann-Whitney test.

Mild NRS 1-3 n (%)	Moderate NRS 4-6 n (%)	Severe NRS 7-10 n (%)	*P*-value*
3 (0.7)	53 (12.9)	354 (86.1)	0.12
156 (37.1)	61 (14.5)	20 (4.8)	<0.01
126 (34.1)	33 (8.9)	10 (2.7)	<0.01
106 (25.3)	36 (8.6)	33 (7.9)	<0.01
11 (9.6)	29 (25.2)	72 (62.6)	0.46
			0.45
			0.33
			0.15
			0.55

Mild NRS 1-3 n (%)	Moderate NRS 4-6 n (%)	Severe NRS 7-10 n (%)	*P*-value*
3 (0.6)	61 (11.4)	471 (87.9)	0.66
217 (40.0)	81 (14.9)	39 (7.2)	0.36
178 (36.3)	62 (12.6)	18 (3.7)	0.44
146 (27.1)	45 (8.3)	54 (10.0)	0.33
15 (9.1)	43 (26.2)	100 (61.0)	0.77
			<0.01
			0.58
			>0.99
			0.61

			Hours from ADP to EBP ≥72 (n=295)					
Mild NRS 1-3 n (%)	Moderate NRS 4-6 n (%)	Severe NRS 7-10 n (%)	n	None NRS = 0 n (%)	Mild NRS 1-3 n (%)	Moderate NRS 4-6 n (%)	Severe NRS 7-10 n (%)	Overall test‡ *P*-value
1 (0.6)	19 (10.4)	162 (89.0)	290	1 (0.3)	1 (0.3)	36 (12.4)	252 (86.9)	0.79
67 (36.6)	26 (14.2)	21 (11.5)	291	127 (43.6)	112 (38.5)	34 (11.7)	18 (6.2)	0.02
60 (35.9)	25 (15.0)	9 (5.4)	260	142 (54.6)	90 (34.6)	21 (8.1)	7 (2.7)	<0.01¶
53 (29.0)	22 (12.0)	21 (11.5)	290	181 (62.4)	72 (24.8)	17 (5.9)	20 (6.9)	<0.01#
4 (5.8)	23 (33.3)	38 (55.1)	44	1 (2.3)	7 (15.9)	13 (29.5)	23 (52.3)	0.12
			21	7.1% (21 of 295)				<0.01~
				48 (34-68)				0.73
				14.3% (3 of 21)				0.16
				52.4% (11 of 21)				0.5

 # At 24hrs, the group ≥72hrs had significant lower pain intensity compared to the group <48hrs (P<0.01) and the group 48 to <72hrs (P<0.01). No significant difference in pain intensity between the groups <48hrs vs. 48 to <72hrs (P=0.59). Statistical method was Mann-Whitney test.

~ The group with ≥72hrs had significant fewer second EBP compared to the group <48hrs (P<0.01) and compared to the group 48 to <72hrs (P<0.01). The group with 48 to <72hrs had significantly fewer second EBP compared to the group with <48hrs (P<0.01). Statistical method was χ^2 test or Fischer exact test when appropriate.

Table 5S. Orthostatic headache defined as delta pain intensity upright vs. supine difference ≥2 NRS units in migraine and non-migraine groups.

n=643	Previous history of Migraine				
	Yes (n=98)		No (n=545)		
	n	%	n	%	*P*-value*
Orthostatic headache†					
6-12hrs before EBP	83 of 94	88.30%	472 of 536	88.10%	0.95
After EBP	30 of 98	30.60%	181 of 543	33.30%	0.6
4hrs after EBP	22 of 85	25.90%	125 of 489	25.60%	0.95
24hrs after EBP	27 of 97	27.80%	131 of 539	24.30%	0.46

Abbreviations: NRS, numeric rating score; EBP, epidural blood patch; ADP, accidental dural puncture.
** χ^2 test as statistical method.*
† Orthostatic headache defined as delta pain intensity upright vs. supine difference ≥2 NRS units

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Chapter 10

Postdural puncture headache: Beyond the evidence

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ABSTRACT

Despite advances in procedural techniques and equipment, postdural puncture headache (PDPH) remains a serious complication of labour epidural analgesia after accidental dural puncture (ADP). Often considered a temporary inconvenience, PDPH can be debilitating in the short term. It can also be associated with chronic manifestations and serious complications.

The precise underlying mechanisms of PDPH are still incompletely understood, and long-standing beliefs of dysregulation of cerebrospinal fluid (CSF) homeostasis due to CSF fluid loss are currently being challenged. The existence of orthostatic headaches unrelated to CSF loss demands consideration of other mechanisms involved, for instance, related to the autonomic nervous system or the release of calcitonin gene-related peptide (CGRP) associated with activation of the meningeal and cerebral arteries.

A multi-society international working group recently provided evidence-based recommendations on the prevention, diagnosis, and management of PDPH resulting from neuraxial procedures. According to the recommendations, there was insufficient evidence to support the routine use of intrathecal catheters or sphenopalatine ganglion blocks to prevent or treat PDPH. Both evidence-based and experimental strategies include stabilizing CSF dynamics through preventing CSF loss, supplementing CSF, or increasing production, and reducing cerebral vasodilation.

Future research in PDPH preventive and therapeutic strategies can be facilitated with standardised definitions, interventions, and outcome measures. Analyses should consider various confounding factors and recognise the complex multifactorial nature of pain experience across diverse populations. Clinical care and research on PDPH will demand a multidisciplinary collaborative effort to elucidate the complexities of its pathophysiology and further improve patient outcome and quality of care.

INTRODUCTION

Postdural puncture headache (PDPH), occurring after intentional or accidental dural puncture (ADP), remains a significant challenge in obstetric anaesthesia due to the high proportion of neuraxial techniques, and prevalence of risk factors such as younger age and female sex. While PDPH has traditionally been considered a relatively benign, self-limited condition, cohort and case-control studies suggest an association between PDPH and long-term morbidities, such as chronic headache, backache, neck pain and depression [1]. Additionally, studies demonstrate an association between PDPH and rare but serious complications such as intracranial subdural hematoma and cerebral venous thrombosis [2,3].

Unfortunately, our understanding of PDPH is incomplete. There is a paucity of high-quality evidence to support many existing management strategies [4]. It is not feasible to conduct sufficiently powered prospective studies for which large numbers of patients would be needed, and ethical considerations prevent randomisation [5]. Here we review the current understanding of PDPH including strategies for prevention, pathophysiology, treatment, and long-term concerns with inclusion of lesser-known strategies for which further research is warranted.

PDPH definition, epidemiology, and diagnosis

a. Definition

The International Classification of Headache Disorders, ICHD-3, classifies PDPH (7.2.1) as a headache developing within 5 days of lumbar puncture, caused by cerebrospinal fluid (CSF) leakage through the dural puncture, which remits spontaneously within 2 weeks, or after sealing of the leak with autologous epidural lumbar patch [6]. As with other headaches caused by low CSF pressure, headache symptoms may be more severe in the upright position (orthostatic or postural), but this feature is not required for a PDPH diagnosis. A PDPH is frequently accompanied by neck stiffness, tinnitus, photophobia and/or nausea. In anaesthesia practice or after diagnostic lumbar puncture, the diagnosis of PDPH is based on clinical symptoms, without the need to confirm reduced CSF pressure or CSF leakage through imaging.

b. Epidemiology

The incidence of PDPH varies based on procedure, needle type, and patient population [7]. Patient-related risk factors for PDPH include female gender, younger age, low body mass index, chronic headache, pregnancy, vaginal delivery, and history of PDPH [4,8]. A PDPH occurs after 50-60% of spinal techniques when large (<24G) cutting spinal needles are used, but this risk falls dramatically to 0.16-2% with the use of pencil-point needles or smaller (>24G) cutting needles [9]. Accidental dural puncture with a large (16-18G) epidural needle results in PDPH in 50-80% of cases [10,11]. With increasing utilization of labour epidural analgesia,

it has been estimated that up to 15,000 women in Europe and 50,000 in the United States develop PDPH after childbirth every year [12,13].

c. Clinical presentation and diagnosis

The presentation of a PDPH is typically dull, throbbing, and bilateral, often with worsening in the upright position. However, up to 5% of PDPH may present without orthostatic changes [14]. Common symptoms include neck stiffness, nausea, vomiting, tinnitus, hearing changes, photophobia, visual disturbances, and vertigo [12]. These symptoms are thought to be the result of descent of brain tissue, engorgement or activation of meningeal or cerebral vessels, meningeal inflammation and temporary dysfunction of the first three cervical and cranial nerves [4,15]. Auditory symptoms, reported in 20% of cases, result from either involvement of the vestibulocochlear nerve or cochlear dysfunction [16].

Table 1. Differential diagnosis of headaches in the postpartum period.

Condition	Common Presentation
Tension headache	Bilateral, tightening headache
Migraine headache	Unilateral, pulsating headache
Preeclampsia with severe features/eclampsia	Headache associated with hypertension or seizure attributed to preeclampsia
Posterior Reversible Encephalopathy Syndrome (PRES)	Headache, visual disturbances, altered mentation, hypertension, ± seizure
Cerebral venous thrombosis (CVT)	Severe headache of gradual onset, typically non-positional
Meningitis/sepsis	Severe headache, fever, nuchal rigidity, vomiting, + Kernig or Brudzinski's sign
Subdural hematoma (SDH)	Progressively worsening headache, with possible decreased consciousness
Postdural puncture headache (PDPH)	Fronto-occipital headache, often worse when upright
Cerebral venous infarction +/-	Headache, focal neurologic deficits
Intracerebral or subarachnoid haemorrhage (SAH)	Headache with focal neurologic deficits, "worst headache ever" (SAH)
Idiopathic intracranial hypertension	Headache, visual symptoms, ± nausea
Reversible cerebral vasoconstriction syndrome	Thunderclap headache

Postpartum headaches are common, affecting approximately 40% of women, with the majority being classified as tension headaches or migraines (Table 1) [17]. It is crucial to consider other potential causes when assessing postpartum headaches. In cases where hypertension is present, new-onset or worsening preeclampsia should be evaluated as a possible diagnosis. Such headaches may involve posterior reversible encephalopathy

syndrome (PRES), though this is rare. Severe and rapidly worsening headache symptoms, especially when accompanied by focal neurological signs or altered consciousness, require immediate neurological assessment and neuroimaging to rule out rare but potentially life-threatening conditions, such as subarachnoid haemorrhage, subdural hematoma, cerebral venous thrombosis, ischemic stroke, or an undiagnosed intracranial tumour [17-20]. To aid in the accurate diagnosis of postpartum headaches, Lim et al. recommend using the PARTUM mnemonic (Table 2) [19].

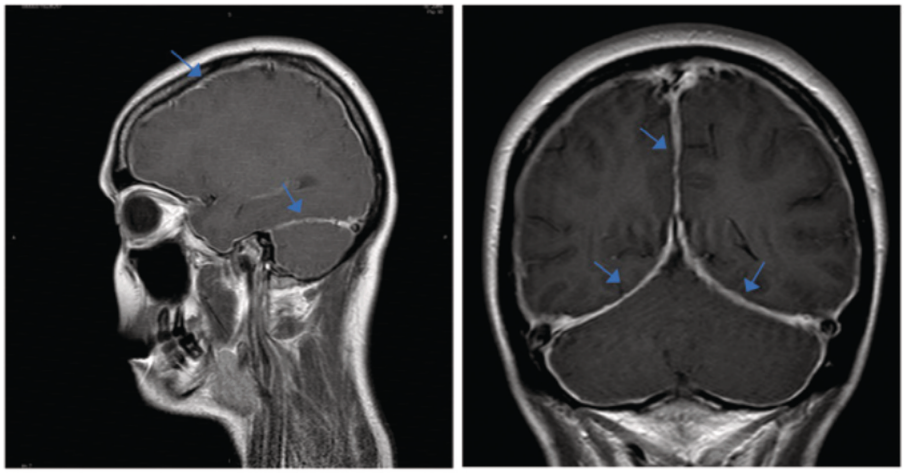
Table 2. PARTUM mnemonic for diagnosis of postpartum headaches. Adapted from Lim et al [19]

P	Pressure	Blood pressure for pre-eclampsia/eclampsia
A	Anaesthetic	Postdural puncture headache (PDPH)
R	Reversible	Reversible vasoconstriction syndrome or posterior reversible encephalopathy syndrome (PRES)
T	Thrombosis	Cerebral venous sinus thrombosis (CVT), ischemic stroke
U	Use your brain	There are so many other causes of headache: musculoskeletal, tension-type, meningitis, caffeine withdrawal, etc.
M	Migraine	if it improved during pregnancy, likely to recur in the first week postpartum

Although PDPH has often been described as self-limiting, early studies reported chronic headache after spinal anaesthesia and recent cohort and case-control studies in obstetrics describe an increased risk of chronic headache, backache, postpartum depression and post-traumatic stress disorder (PTSD) [21-23]. A recent anonymous online survey of individuals on a PDPH-patient advocacy website reported severe long-term consequences such as persistent headache and disability in patients previously diagnosed and treated for PDPH after lumbar puncture, epidural anaesthesia, or spinal surgery [24]. Given the retrospective nature of data on chronic headache after PDPH, the possibility of bias is significant [23]. Nonetheless, mounting evidence for an association of PDPH with chronic headache and other sequelae warrant further attention and consideration for longer-term follow-up.

In obstetric PDPH, additional diagnostic tools [e.g., radiologic evidence of CSF leak or lumbar puncture demonstrating CSF pressure <60 mm H2O)] are not typically used, and PDPH remains a clinical diagnosis [4]. If the headache presentation is atypical, changes over time, or symptoms appear which cannot be explained by CSF loss or raise suspicion of serious complications, then imaging is warranted [4]. Neuroimaging can rule out other pathology and either directly or indirectly demonstrate signs of CSF leakage. Spinal MRI, CT, or digital subtraction myelography can display the amount and site of CSF leakage. However, this finding can be nonspecific, often unaccompanied by clinical PDPH symptoms, or clinical symptoms can be present without signs of spinal CSF leakage [25,26]. Cranial MRI using a gadolinium-based contrast agent may show pachymeningeal (dural) enhancement, venous engorgement, brain sagging, or pituitary enlargement. In one study, 100% of patients undergoing MRI within 3 days of PDPH onset showed dural enhancement (Fig. 1) [27].

Fig. 1. Brain MRI: Pachymeningeal enhancement (arrows)



A B

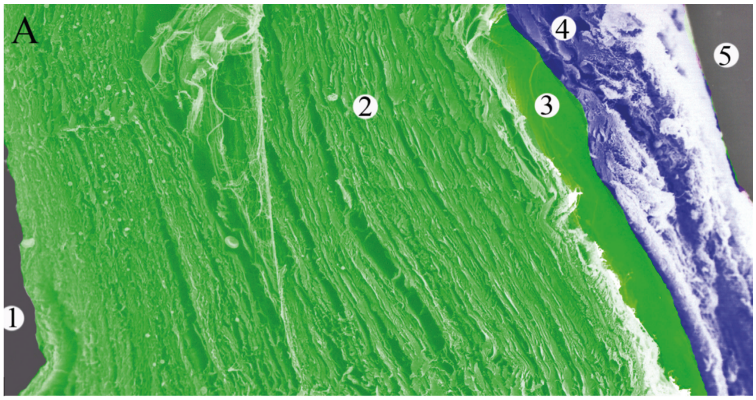
(A) Sagittal gadolinium-enhanced TSE, T1-weighted brain MRI.
(B) Coronal gadolinium-enhanced TSE, T1-weighted brain MRI.
From: Brain MRI features of postdural puncture headache, Sanchez Garcia et al., Reg Anesth Pain Med 2024 [27].

Transorbital ultrasound for optic nerve sheath diameter (ONSD) measurement could possibly aid in the diagnosis and monitoring of PDPH, as changes in CSF pressure are transmitted along the optic nerve sheath [28]. Increased ONSD has been demonstrated after successful epidural blood patch (EBP) or closure of CSF leaks and is associated with a decrease in intracranial venous volume and blood flow [28,29].

The pathophysiology of PDPH

Postdural puncture headache (PDPH) was first accurately described by Dr. August Bier in 1899, who linked the condition to CSF loss and emphasized minimizing CSF loss during procedures. A similar orthostatic headache can occur with spontaneous intracranial hypotension (SIH), even without prior trauma or medical intervention [30]. The CSF leak is often perceived to result from a dural tear; however, the primary barrier preventing CSF leakage is not the dura mater, with its 70-80 permeable layers of randomly arranged collagen and fibrinogen fibres, but rather the impermeable arachnoid mater (Fig. 2) [31].

Fig. 2. Human dura and arachnoid mater thickness.



Dura mater in green and arachnoid mater in blue
Magnification A: x300
(1) Epidural space; (2) Dura mater; (3) Acquired subdural space; (4) Arachnoid mater; (5) Subarachnoid space.
With permission from Prof. Miguel A. Reina M.D., Ph.D., private archive.

When spinal CSF loss exceeds the body's replacement rate (estimated to be about 300-1000 mL/day), the reduction in intracranial CSF volume—and eventually pressure, once the compensatory cerebral vasodilation capacity is surpassed—can cause a downward shift of brain structures, known as brain sagging [32,33]. This phenomenon can be accentuated in the upright position. The headache symptoms are thought to relate in part to traction on pain-sensitive structures such as meninges, arteries near the base of the brain, and anchoring veins draining into the sagittal, transverse, and other venous sinuses [34-36].

Another feature of PDPH appears to involve cerebral vasodilation, as a *reflex response* to traction on intracranial pain-sensitive vessels and/or a *compensatory mechanism* caused by a reduction in CSF volume. This compensatory mechanism of haemostatic intracranial volume regulation (Monro-Kellie doctrine) is displayed when a loss in intracranial CSF volume is accompanied by an increase in cerebral blood volume (via vasodilation) [33,37].

Dilation of the meningeal arteries and activation of the trigeminovascular system (TVS) involving release of calcitonin gene-related peptide (CGRP) may also contribute to headache symptoms like those of migraine headaches [33,38]. Another hypothesis suggests that lumbar CSF loss increases spinal compliance caudally, leading to low intracranial CSF pressure in the upright position, and subsequently to intracranial venous dilation [39-41]. Lastly, neurotransmitters and modulators involved in pain perception, such as substance P, may play a role. Reduced CSF levels of substance P have been associated with an increased incidence of PDPH following lumbar puncture [42].

It is notable that orthostatic headaches can occur without CSF disturbances in autonomic nervous system (ANS) dysfunction syndromes like orthostatic hypotension or postural orthostatic tachycardia syndrome (POTS), when compensatory baroreflex mechanisms fail to adapt to postural changes [43,44]. In over 40% of cases, POTS coexists with other headache disorders, such as migraine or SIH, or develops after successful SIH treatment, which suggests a contribution of autonomic dysfunction [43-45]. Further research is needed to elucidate the ANS mechanisms involved in the evolution of PDPH, and to identify potential therapeutic targets that modulate this activity.

Current evidence-based preventive and therapeutic management strategies for PDPH

a. Summary

The rare occurrence of PDPH and variability in clinical presentation make gathering of high-quality evidence difficult. Recently, a multidisciplinary group published expert- and evidence-based recommendations using the US Preventative Services Task Force grading guidelines [46]. Recommendations assigned levels of certainty give clinicians a framework for the prevention, identification and management of PDPH (Table 3) [4,46]. The main procedural recommendation for spinal anaesthesia/analgesia or lumbar puncture to minimize the risk of PDPH is to use a high gauge (small calibre), pencil point needle whenever feasible [4,47]. There is currently insufficient evidence to support other suggested preventative strategies, such as particular patient or needle positioning, postprocedural bed rest, hydration, or medications [4].

Intrathecal insertion of the epidural catheter (intrathecal catheter, ITC), once an accidental dural puncture (ADP) occurs, may provide a functional mode of labour analgesia or caesarean delivery anaesthesia, but does not decrease the risk of PDPH and/or the need for an EBP [4]. Likewise, the neuraxial injection of other substances (e.g., preservative free morphine, saline) into the epidural space or the use of prophylactic EBPs have not consistently shown benefit [4,48].

Once PDPH develops, recommended conservative management includes maintenance of adequate hydration and the provision of a multimodal analgesic regimen including paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), and limited use of opioids [4]. Oral caffeine may temporarily reduce symptom severity, but the ingested amount should be limited in obstetric patients and breastfeeding women [4]. While maintaining the supine position reduces the severity of symptoms and provides temporary relief, prolonged bedrest is undesirable due the increased risk of thrombosis associated with immobility [4]. Of the more invasive procedures for PDPH treatment, limited evidence suggests that a greater occipital nerve block (GONB) might be considered after spinal anaesthesia with small gauge spinal needles [4,49]. The EBP is the most effective invasive procedure for providing temporary or permanent relief from PDPH resulting from various dural

puncture interventions. It should be considered in patients with PDPH that is impairing the activities of daily life and that does not respond to conservative therapies [4].

Table 3. Consensus practice guidelines: preventive and therapeutic measures with level A-C grading recommendations.

	Recommendation Level	
Procedural factors		
Non-cutting spinal needles	A	
Narrower gauge cutting spinal needles	A	
Conservative treatments		
Paracetamol (acetaminophen) and NSAIDs offered to all patients with PDPH	B	
Short-term opioid use if regular analgesics ineffective	C	
Caffeine offered in the first 24 h of symptoms	B	Maximum dose of 900 mg/day, 200-300 mg if breastfeeding
Adequate hydration maintained with oral fluids	C	
Bedrest to lower severity of symptoms	C	Beware of increased risk of thromboembolism
Invasive treatments		
Greater occipital nerve block (after spinal anaesthesia with 22-G or smaller spinal needle)	C	Headache recurrence risk
Epidural blood patch	B	Offered if PDPH does not respond to conservative treatment and impairs daily activities

Adapted from: Uppal et al. [4]
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; PDPH, postdural puncture headache; mg, milligrams; G, gauge

b. The epidural blood patch (EBP)

The EBP has been the cornerstone of PDPH treatment, since Gormley observed that bloody taps during spinal anaesthesia were associated with a lower PDPH incidence. An EBP involves the injection of autologous blood into the epidural space, with a hypothesized two-fold effect: increasing epidural and lumbar CSF pressure and stimulating fibroblastic repair in proximity to the dural defect. The immediate but transient increase in epidural volume increases the spinal and intracranial CSF pressure. Notably, there is no demonstrated relationship between the final epidural pressure generated during the procedure and its success [50,51]. An epidural

hematoma is known to be a potent cerebral vasoconstrictor which may contribute to the positive outcome [38,51]. MRI studies have shown that the mass effect of injected blood lasts only a few hours, and clot forms within 7 h, which stimulates fibroblastic and collagen repair of the dural defect, preventing further CSF leakage [52-54]. Absolute contraindications for an EBP are patient refusal, coagulopathy (thrombocytopathy, active anticoagulation), sepsis, systemic infection without CNS involvement, local infection at the site of injection, and increased intracranial pressure [4,55,56].

Efficacy of an EBP procedure varies significantly, likely reflecting procedural and patient-related factors and the extent of dural damage. For PDPH after spinal anaesthesia, EBP success rates of 75-96% have been reported. After ADP with large gauge Tuohy needles in obstetrics, complete and permanent resolution of symptoms after one EBP occurs in less than 50% of patients [4,56,57]. A large prospective international cohort study of 647 obstetric patients (EPiMAP) investigating risk factors for EBP failure after ADP found that complete success (defined as an NRS score of 0 in upright position at 4, 24 and/or 48 h) was achieved in only 33.0% of cases [58]. Complete failure (NRS scores ≥7 at one of these time points or the need for a second EBP) occurred in 28.7% of patients, with 19.8% ultimately requiring a second EBP [58].

The optimal volume and timing of an EBP is unknown. The EPiMAP study could not provide a definitive answer as most patients received approximately 20 mL of blood, according to common practice [58,59]. The study found no association between EBP failure and EBP lumbar level, position during EBP, or operator experience. The only associations with failure of EBP were timing of the EBP, a history of migraine which was specifically associated with an increased provision of a second EBP, and (unexpectedly) a higher lumbar level of the original ADP.

As reported, the EPiMAP study confirmed that patients receiving an early EBP, within 48 h after ADP, were more likely to require a repeat procedure: 37.8% of women who received an EBP within 48 h of the ADP needed a second EBP, compared to 23.4% who received their first EBP between 48 and 72 h, and 7.1% after 72 h. Importantly, it is not known whether receipt of an earlier EBP was associated with more severe presenting PDPH symptoms [4,56,58]. These findings suggest that if an early EBP is recommended to patients, they should be informed of the possibility of a repeat EBP to achieve complete resolution of symptoms [4]. However, delaying an EBP for patients with severe symptoms is not recommended, as it prolongs patient suffering and may increase the risk of rare severe complications such as subdural hematoma [3].

The most common reported complication of EBP is back pain, with an estimated incidence of 80%. Chronic headache, present a year after ADP in 28% of patients, is not significantly reduced in patients who were treated with an EBP [57,60]. Arachnoiditis, radiculitis, meningitis and spinal subdural hematoma, all serious neurologic conditions, have been described both after ADP alone, and after EBP [61-63].

Alternative current and future management strategies

Over the years clinicians have explored numerous additional interventions to prevent and treat PDPH based on the presumed pathophysiological mechanisms described above. Sufficient evidence is lacking to promote their recommendation for routine use.

a. Reducing cerebrospinal fluid leakage with an ITC

There appears to be no consistent association between the volume of CSF loss and the degree of PDPH symptoms, and interindividual variability is significant. Some patients develop severe symptoms after an uneventful procedure with a 27 G pencil-point needle, while others remain asymptomatic even after ADP with a large bore epidural needle. Transient headache symptoms do often occur during drainage of CSF in lumbar punctures and are associated with the volume collected. However, headache immediately after lumbar puncture procedures is unrelated to persistent PDPH at 24 h or the need for an EBP [36,64].

One intervention to reduce CSF loss following ADP during epidural labour analgesia procedure is the immediate insertion of an intrathecal catheter (ITC). The ITC can be used to provide rapid labour analgesia without the need for another procedure and is thought to potentially reduce CSF leakage by partially occluding the dural hole. An ITC should only be considered in the presence of an institutional protocol which includes strict aseptic techniques, meticulous monitoring, labelling and communication to prevent drug errors, and recommendations of drugs and dosages to be used intrathecally under the various obstetric scenarios [65,66]. Although several studies and meta-analyses have suggested that ITCs reduce PDPH severity and EBP use, Heesen et al.'s trial sequential analysis determined evidence to be insufficient to exclude a type 1 error (false positive, rejecting the null hypothesis when it is actually true), despite finding a reduced PDPH incidence (RR 0.82, 95% CI 0.71-0.95) and need for EBP (RR 0.62, 95% CI 0.49-0.79) [5]. Two subsequent retrospective studies have suggested benefits of ITC, with or without intrathecal saline administration [67,68]. One showed no additional benefit in leaving the ITC in place postpartum [68]. Notably, the best practices outlined in the 2024 Guidelines on ITC placement after ADP from the Obstetric Anaesthetists' Association conclude that there is no evidence-based indication for leaving the ITC in situ after delivery is complete [66].

b. Increasing cerebrospinal fluid volume

Various strategies aim to increase the production of CSF. Increased fluid intake, administration of caffeine or other methylxanthines, hydrocortisone and ACTH-analogues, have all been considered but have not proven to contribute to increased CSF production [4]. There is currently renewed interest in the ACTH-analogue cosyntropin, which is hypothesized to contribute to analgesia and increased CSF production through stimulation of glucocorticoid and mineralocorticoid synthesis [69]. However, the results of studies demonstrating cosyntropin's effectiveness in preventing PDPH or reducing its severity are inconsistent. A randomized controlled trial in obstetric patients after ADP did find that cosyntropin reduced

the incidence of PDPH and the need for an EBP compared to placebo [70]. In a retrospective study of 578 women with ADP, the combination of cosyntropin, an ITC, and prophylactic administration of 10 ml intrathecal (IT) saline did not reduce the incidence of PDPH, but did decrease the need for an EBP [68,71]. Other recent retrospective analyses failed to find any benefits from the use of cosyntropin in preventing or reducing severity of PDPH [69,72].

Epidural single shot saline boluses and continuous epidural or caudal saline infusions have been used as an option for the treatment of PDPH. Sterile saline, injected epidurally, produces a short-lived mass effect which is thought to temporarily reduce CSF flow through dural hole, thus facilitating repair [73]. One study demonstrated that epidural saline injections resulted in either resolution or temporary relief of PDPH after spinal anaesthesia, even though there was only a 3-to-10-min increase in epidural and subarachnoid pressure, depending on volume, injection rate and site of injection [50]. Various regimens in different patient populations have been studied, and while severity of symptoms reduces, the effect is transient, compared to EBPs [4,73].

IT saline injection may relieve stretching of pain-sensitive structures and secondary vasodilation. Intrathecal injection of saline, either during a spinal procedure, during ADP, or through an ITC before removal, appears to contribute to reduced incidence and severity of PDPH, though current evidence is not sufficient to recommend this as standard practice [4,67,68].

c. Reduction of cerebral vasodilation

Various treatments for migraine and cluster headache, such as triptans, gabapentinoids, sphenopalatine ganglion block (SPGB), and greater occipital nerve block (GONB), have shown some effectiveness in relieving the symptoms of PDPH, suggesting potential similarities in underlying pathophysiologic mechanisms. Interruption of central sensitization, reduction of inflammation, and modulation of pain pathways may contribute to relief of symptoms [74]. Likely, cerebral vasoconstriction is an important mechanism of action. For example, sumatriptan is thought to inhibit presynaptic serotonin release which reduces cerebral vasodilation and interferes with vasoactive peptides release and trigeminal pain [75-77]. There is insufficient evidence to recommend caffeine and other xanthine derivates such as aminophylline or theophylline, although a recent meta-analysis found the last two medications associated with lower pain scores [4,78]. A prospective randomized controlled study showed that neostigmine in combination with atropine reduced the severity of PDPH and accelerated recovery, while nebulized dexmedetomidine significantly reduced PDPH severity and reduced mean flow velocity in the middle cerebral artery of postpartum patients [79,80]. Further exploration of these therapies for PDPH are warranted.

d. Peripheral nerve blocks to modulate the pain pathway

The SPGB, typically used in patients with cluster headache and trigeminal neuralgia, is considered to be a minimally invasive alternative treatment option for PDPH [38,81]. The

sphenopalatine ganglion (SPG) is the main extracerebral parasympathetic ganglion, located bilaterally in the pterygopalatine fossa, containing sensory, sympathetic, and parasympathetic fibres that innervate the lacrimal glands, nasal glands, and cerebral blood vessels [82]. The SPG is connected to the trigeminovascular system, which is implicated in various headache disorders. While its mechanism of action is not fully elucidated, the SPGB appears to temporarily reduce or reverse cerebral reflex vasodilation due to low CSF volume and potentially interrupt trigeminal activation, or modulate inflammatory neurotransmitters involved in pain signalling [38,82]. The precise mechanism is not completely understood, as an RCT has demonstrated that a SPGB with saline is as effective as LA in reducing headache symptoms and the need for an EBP in patients with PDPH after intended or ADP [83]. An effective SPGB typically provides only temporary symptomatic relief, and repeated treatments may be necessary before PDPH symptoms resolve [84]. Techniques include percutaneous and trans-nasal approaches, the latter being the less invasive, but likely less effective as well [38,85]. Although there is insufficient high-quality evidence to support the routine use of SPGB for PDPH, it may be an alternative strategy when EBP is contraindicated or refused. Further refinement and standardization of this less invasive technique may increase its utility [85].

The GONB has been shown to effectively reduce PDPH severity in patients with PDPH after spinal anaesthesia with a traumatic needle and might be effective after ADP [4,49]. A typical GONB includes bilateral injection of local anaesthetic and corticosteroid near the greater occipital nerves and may modulate trigeminocervical signalling to effect central pain processing pathways. The anti-inflammatory effect of the corticosteroid dose may augment the efficacy of the GONB. Other medications with similar actions are gabapentin which might reduce headache severity through modulating pain pathways, and hydrocortisone with its anti-inflammatory properties [86].

e. Oxygen therapy

Oxygen therapy can be effective in treatment of cluster headache where it may have similar actions as in high altitude headache: inhibiting trigeminal-vascular and autonomic pathway innervation by acting specifically on the PS/facial nerve projections to the cranial vasculature [87]. One small retrospective study described the use of high flow oxygen in conjunction with metoclopramide as a pro-serotonin agent to treat PDPH resulting from various diagnostic and therapeutic lumbar punctures [88]. In 10 out of 12 patients, PDPH symptoms resolved rapidly, without additional metoclopramide administration [88].

Overall, while cerebral vasoconstriction is considered to be the primary mechanism of action of these therapies, central sensitization interruption, anti-inflammatory effects, and pain pathway modulation may have additional important effects.

f. Promotion of dural healing

In treatment resistant PDPH, other means of repairing the meningeal breach have historically been considered, such as the use of fibrin glue. While the limited evidence present does not support routine use, and complications include anaphylaxis and aseptic meningitis, a 2024 prospective, randomized non-blinded study in 70 obstetric patients with refractory PDPH after ADP compared EBP with epidural fibrin glue injection (6 mL fibrin sealant (Tissucol Duo®, Baxter S.L. Valencia, Spain) [4,89]. Epidural fibrin glue injection resulted in 100% complete relief at 12 h and at 30 days, compared to an EBP (15 mL blood) which only provided complete relief in 65.7% of patients at 12 h and in 22.9% at 30 days [89]. The most common complication, lumbar radiculopathy, occurred 6 times more frequently in the EBP group which also had a significantly longer hospital stay.

CONCLUSION

The unpredictable occurrence and the variety in signs, symptoms, and severity of PDPH suggest additional patient risk and mechanistic factors, which require further investigation. To date, our understanding of PDPH has relied on retrospective or small cohort studies hindered by variable definitions, heterogeneous strategies, and inconsistent outcomes. Pain outcomes may be impacted by individual, societal, social, and culturally determined factors. Variable timing of interventions, placebo effects, and the spontaneous resolution of symptoms can introduce confounding. Lastly, there are ethical issues preventing optimal study design, such as randomisation to include using larger or cutting needles for dural puncture, or withholding treatment with an EBP, given the lack of equipoise in these strategies as they relate to PDPH risk and treatment.

The path forward requires a multidisciplinary, international effort by experts from anaesthesiology, neurology, neuroradiology, neurosurgery, pain medicine and basic science. Use of a Delphi method could achieve consensus on a global, standardized definition of PDPH, diagnostic criteria and identification of outcome measures. Collaboration on studies should address both fundamental mechanisms and clinical challenges. A multi-centre PDPH registry could provide a method to collect comprehensive data on PDPH cases, and integrate patient reported outcomes and experiences to capture the full impact of PDPH. In this manner, we can meaningfully work to improve the quality of our care related to ADP, an important complication of neuraxial procedures.

Research agenda

Investigate potential strategies to reduce ADP during epidural procedures.

Develop standardized definitions and diagnostic criteria for PDPH and therapeutic outcome measures.

Develop a multi-center PDPH registry to collect prospectively relevant data.

Evaluate the role of new diagnostic tools such as optic ultrasound in PDPH diagnosis and treatment.

Design a multi-center RCT comparing treatment strategies for PDPH after ADP.

Practice points

Pencil-point spinal needles should be used for neuraxial procedures worldwide, as they significantly reduce PDPH incidence

Postpartum headaches should be systematically evaluated to differentiate PDPH from both more benign and more serious causes

If a PDPH does not respond to conservative measures, an EBP should be recommended

An EBP is the most effective treatment for PDPH, but a repeat EBP might be necessary to achieve complete resolution of symptoms

An ITC should only be considered in the presence of strict institutional protocols to ensure safe use

When an EBP is contraindicated of refused, alternative strategies like a SPGB or GONB can be considered

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Chapter 11

Summary and perspectives

In pregnant patients, when surgical interventions are needed or labour analgesia is requested, neuraxial techniques are preferred over inhalation and intravenous anesthesia whenever possible. Depending on the dose administered, epidural and spinal local anesthetics block sensory nerve transmission to provide analgesia or even complete anesthesia to the lower body. During surgical interventions, neuraxial anesthesia will avoid the need for general anesthesia and prevent the potential occurrence of airway problems which happen more often during pregnancy. As the LA doses needed to act at the neuraxial target are small and do not lead to clinically relevant plasma concentrations, they minimize fetal drug exposure. Opioids added to the LA solution facilitate reduction of LA doses and further improve analgesia. When long-acting opioids are incorporated in the spinal anesthetic mixture for cesarean delivery, postoperative pain relief is also optimized, which potentially contributes to the prevention of chronic postsurgical pain. And last but not at all least, as these techniques do not interfere with maternal awareness or consciousness, they allow the woman to participate and experience the birth of her child during cesarean delivery.

Potential disadvantages of neuraxial techniques

Motor block

Neuraxial techniques come with their own set of drawbacks, as not only sensory, but motor and sympathetic nerve fibers are affected. While motor block is beneficial during surgical procedures under spinal anesthesia, it could impair maternal pushing efforts during the second stage of vaginal delivery when epidural analgesia is used. Indeed, in the past, higher concentrated LA solutions correlated with increased instrumental delivery rates, which was attributed to maternal motor weakness. Whether direct interference with uterine contractility also contributed to this correlation, remains unknown as it is difficult to investigate using non-invasive uterine monitoring techniques. With the currently used low-concentrated epidural LA solutions there appears to be no longer an increased incidence of instrumental deliveries, but a slight prolongation of first and/or second stage of labour is still observed, and an increased association with oxytocin augmentation persists.

Postspinal hypotension

Neuraxial administered LA spreads cephalad, depending on technique and LA dose, which disrupts sympathetic neural transmission to a greater or lesser extent. The resulting maternal vasodilation and ensuing hypotension may cause nausea, dizziness, fetal acidosis and bradycardia, and in severe cases even lead to maternal cardiovascular collapse. During initiation of spinal anesthesia, patient-specific titration of the LA dose can mitigate this so-called postspinal hypotension, which affects up to 90% of women in absence of prophylactic measures such as fluid co-loading and vasopressor infusion.

Postdural puncture headache

One of the main original objections to spinal anesthesia was the severe postural headache which initially developed postoperatively in up to 40% of patients, which often lasted several

days and complicated recovery. Resulting from puncture of the spinal dura/arachnoid membrane with a sharp cutting spinal needle and the ensuing leakage of cerebrospinal fluid (CSF) into the epidural space, improved needle design has decreased the severity and reduced the incidence of PDPH after spinal anesthesia to around 1%. In obstetric anesthesia though, it remains a significant challenge, especially when epidural analgesia techniques are used, and the epidural needle is inadvertently advanced too far and accidentally penetrates the dura/arachnoid membrane.

Summary of studies in this thesis

This thesis includes various studies which address a few of the many questions related to spinal and epidural techniques in obstetrics. They investigate the benefits, challenges, or consequences of neuraxial anesthesia and analgesia , in order to contribute to improved anesthetic contribution in maternal clinical care.

In chapter 2 of this thesis, a novel monitoring technique to determine uterine activity, electrohysterography (EHG), is used to study the influence of epidural analgesia initiation on uterine contraction frequency during active labor. The new technique performs reliably, identifying a statistically significant but clinically irrelevant small decrease in contraction frequency. It demonstrates the potential value of electrohysterography monitoring in clinical obstetric practice and research and its applicability in investigating the effects of neuraxial analgesia techniques and other intrapartum interventions.

Chapters 3 and 4 study the incidence of chronic postsurgical pain (CPSP) after cesarean delivery, with or without the addition of intrathecal morphine to the spinal anesthetic mixture (chapter 3), and its potential association with postpartum depression (chapter 4). It is concluded that the addition of morphine does not prevent CPSP, but the pain is significantly associated with postpartum depression.

In chapter 5 a significant association is found between preoperative depression scores and the occurrence of postspinal hypotension during elective cesarean delivery. This raises the hypothesis that the mental status of the woman going into surgery may influence the severity of side effects of neuraxial procedures.

Chapter 6 describes a study to optimize the amount of LA in relation to height and weight for spinal anesthesia in short stature parturient undergoing a cesarean delivery. It turns out that in this specific population of short stature Nepalese parturients, only height was of importance in this respect.

Chapters 7-10 are centered around the EPiMAP[1] study, a prospective cohort study examining management practices and outcomes of Post-Dural Puncture Headache (PDPH) occurring after accidental dural/arachnoid puncture in obstetrics (chapter 8). EPiMAP also investigated factors associated with failure of the often-applied epidural blood patch to resolve PDPH symptoms, a previously unknown association with the level of the original dural/arachnoid breach surfaced (chapter 9). Chapter 7 provides a comprehensive review of post-dural puncture headache (PDPH) characteristics and evidence-based prevention and treatment approaches. Chapter 10 elaborates beyond current evidence, as the presumed underlying mechanisms of PDPH have never been clarified and are based on longstanding beliefs of CSF homeostasis which are currently being challenged by new insights.

Future perspectives

These studies contribute in various ways to our understanding of several aspects of neuraxial analgesia and anesthesia in obstetrics. They address diverse problems: from the use of EHG to identify changes in uterine activity during epidural labour analgesia, to factors influencing the development of chronic postsurgical pain, from reflecting on predictors of spinal anesthesia-induced hypotension, to a comprehensive exploration of PDPH mechanisms and therapies. While the findings contribute to current clinical knowledge, they also highlight important gaps and raise new questions relevant for obstetric anesthesia. Future studies must not only address these questions by building upon these specific findings, but also include recent evidence from other fields of medicine and especially from fundamental basic science.

Obstetric anesthesia is, like other fields of anesthesia and medicine, an ever-evolving art, with science and research continuously providing new insights to optimal anesthesia provision. This thesis shows this evolution through using novel clinical tools such as EHG and potential identification of a previously never observed association between mental status and postspinal hypotension. Yet, clinical anesthesia research unfortunately often fails to question the underlying established fundamental physiological assumptions. Instead, it builds upon age-old traditional theories, as illustrated by our critical examination of PDPH mechanisms which challenges conventional beliefs about CSF homeostasis. It takes years for new findings from adjacent medical fields to permeate anesthesia literature and textbooks, even when they challenge, contradict, and refute these established principles. Our findings on the relationship between postpartum depression and chronic postsurgical pain highlight the importance of multi-disciplinary perspectives. The scientific road ahead requires not only solid evidence but also a relentless cross-disciplinary curiosity that views limitations in contemporary research as invitations to explore unconventional hypotheses. Without this approach, we cannot explain phenomena like why the spinal level of an accidental dural puncture affects epidural blood patch success: a relationship for which current knowledge offers no explanation. Curiosity, together with critical appraisal of current and new understandings of underlying

1 European Practices in the Management of Accidental Dural Puncture

(patho)physiology, of newly developed diagnostic and therapeutic tools, and of contribution of artificial intelligence (AI), will lead to new hypotheses, research questions and eventually new insights in optimal safe clinical care while minimizing potential unintended consequences of our anaesthetic interventions.

Future perspectives in the Netherlands

Dutch obstetric anesthesia stands at a unique crossroads, shaped by our distinctive approach to childbirth compared to other countries. The emphasis on natural birth with minimal interventions, while valuable in many respects, faced scrutiny when 2008 data revealed elevated perinatal mortality rates relative to comparable health care systems. In response, the College Perinatale Zorg (CPZ) was established and the Integrale Zorgstandaard Geboortezorg was developed and implemented to enhance interprofessional collaboration. However, these initiatives insufficiently acknowledged contribution of anesthesiology in ensuring maternal safety, despite anesthesiologists' involvement in approximately 40 % of all deliveries. Subsequent advancements in obstetric anesthesia were mainly driven by efforts of a small but dedicated group of anesthesiologists who identified critical needs for improvement in training, simulation and collaboration, with active daily contribution on the labour ward only realised in the Sophia's Children Hospital of the Erasmus MC. The Dutch Society of Anesthesiology initially demonstrated limited recognition of the importance of enhanced collaboration but is now progressively assuming its responsibility in supporting and expanding these initiatives.

The optimization of obstetric anesthesia necessitates increased integration within clinical obstetric care, proactive participation in multidisciplinary consultations, intensified residency training and representation in key organisations such as the CPZ. Comprehensive evaluation of the quality of currently provided anesthesia services and identification of structural barriers are essential for determining areas in need of improvement. It is not a matter of more, but better provision of anesthesia care!

While these strategic efforts have yet to be initiated, a slow but gradual progress can be observed. Anesthesiologists increasingly contribute to the development of multidisciplinary obstetric guidelines, the first research program measuring quality and outcome measures in caesarean delivery has been established, educational opportunities in obstetric anesthesia are expanding, and anesthesiologists are assuming responsibility for patient education regarding anesthesia procedures and analgetic options.

These developments demonstrate a growing professional commitment to advancing the field of obstetric anesthesia. Main participants and stakeholders in obstetric care should join to address system deficiencies that compromise maternal clinical care. Resolution of financial constraints that impede consistent anesthesiology presence on labour wards, elimination of reimbursement structures that disincentivize appropriate anesthesia staffing,

and implementation of sustainable financial frameworks that acknowledge the critical role of anaesthesiologists in ensuring safe outcomes for both mothers and babies are imperative.

Only by true integration of anesthesiology expertise within the multidisciplinary obstetric care team the needed quality improvements in obstetric anesthesia can be achieved. It not only demands continuing dedication from specialized anesthesiology groups and increased support from professional societies, but also structural, financial and organisational reforms that will enable optimal participation in Integrated birth care.

In conclusion, the research presented in this thesis offers small building blocks toward optimizing obstetric anesthesia care. While continuous methodologically sound research is essential to expand our knowledge, systemic improvements are equally necessary to truly enhance the quality of anesthesia services in Dutch obstetric care. By advancing simultaneously scientific understanding and healthcare delivery we can work toward providing safer and more effective obstetric anesthesia for all women, also in the Netherlands.

Chapter 12

Nederlandse samenvatting

Wanneer tijdens zwangerschap en bevalling chirurgische ingrepen noodzakelijk zijn of pijnverlichting gewenst is, dan genieten epidurale en spinale anesthesie (neuraxiale) technieken de voorkeur. Omdat hierbij geen medicijnen intraveneus worden toegediend (waardoor ze slechts minimaal in de bloedbaan van de moeder terecht komen) blijft de blootstelling van de foetus aan medicijnen en beïnvloeding op de voortgang van de bevalling minimaal.

Neuraxiale toediening van lokaal anesthetica (LA) blokkeert de zenuwgeleiding tussen het perifere en centrale zenuwstelsel, waardoor -afhankelijk van de locatie en de dosering- pijnverlichting of volledige verdoving van het onderlichaam ontstaat. Door toevoeging van opioïden aan de LA-oplossing wordt de pijnstillende werking verbeterd en kan voor epidurale pijnverlichting tijdens de bevalling de concentratie LA verder worden verlaagd. Neuraxiale technieken beïnvloeden echter niet alleen sensorische, maar ook motorische en sympathische zenuwvezels, hetgeen bij onjuiste toepassing tot bijwerkingen en complicaties kan leiden. Bij epidurale pijnstilling tijdens de bevalling veroorzaakten de vroeger gebruikte hogere LA-concentraties een gedeeltelijke motorische blokkade, die tijdens de uitdrijvingsfase de perskracht van de moeder kon belemmeren. Dit risico is echter sterk afgenomen door het gebruik van de huidige zeer laag-geconcentreerde oplossingen. Dit laatste vermindert ook de mate van sympathische zenuwblokkade die vasodilatatie kan veroorzaken. Zonder adequate voorzorgsmaatregelen en afhankelijk van de gebruikte dosering LA kan deze vasodilatatie maternale hypotensie tot gevolg hebben, die gepaard kan gaan met misselijkheid en duizeligheid, en in extreme gevallen zelfs tot foetale acidose en bradycardie leidt.

Een andere ongewenste bijwerking van neuraxiale anesthesie, bij spinale anesthesie niet altijd te voorkomen maar bij epidurale analgesie te beschouwen als een complicatie, is de postdurale punctie hoofdpijn (PDPH). Door bedoelde of accidentele punctie van spinale dura/arachnoïde membranen kan hersenvocht (Cerebrospinal fluid, CSF) lekken naar het epidurale compartiment. Bij sommige patiënten ontstaat hierdoor een houdingsafhankelijke hoofdpijn, die meestal tijdelijk is. Ook nekpijn, oorsuizen, duizeligheid en visusstoornissen kunnen hierbij optreden. Verbeterd naaldontwerp heeft de incidentie van PDPH na spinale anesthesie teruggebracht tot ongeveer 1%, maar het blijft een uitdaging om bij het starten van epidurale analgesie tijdens de bevalling een accidentele durale punctie te voorkomen.

Dit proefschrift onderzoekt niet zozeer de effectiviteit van de pijnstilling tijdens of na de bevalling, maar richt zich op ongewenste aspecten van neuraxiale analgesie en anesthesie in de klinische verloskunde. Het herkennen, voorkomen en/of behandelen van diverse bijwerkingen en complicaties van obstetrische anesthesie komen aan de orde: van de bruikbaarheid van electrohysterografie (EHG) om de mogelijke ongewenste gevolgen van epidurale analgesie te bestuderen tot factoren die mogelijk bijdragen aan chronische postchirurgische pijn na een keizersnede, van voorspellers van spinale anesthesie-geïnduceerde hypotensie tot een uitgebreide verkenning van PDPH-mechanismen en therapieën.

Hoofdstuk 2 gebruikt elektrohysterografie (EHG) om de invloed van epidurale analgesie op het aantal baarmoedercontracties te bestuderen tijdens de bevalling. Electrohysterografie registeert de electrische activiteit van de baarmoeder en is tegenwoordig klinisch beschikbaar om weeën te registreren tijdens de bevalling. Ondanks het gebruik van laag geconcentreerde LA tijdens epidurale analgesie bestaat er nog steeds een associatie tussen epidurale analgesie en een licht verlengde duur van de partus en het gebruik van weeënstimulatie m.b.v. oxytocine. Men kan zich afvragen of oxytocinegebruik leidt tot pijnlijker weeën en daardoor vaker tot een verzoek om pijnverlichting, of dat epidurale analgesie de weeënactiviteit beïnvloedt waardoor er vaker alsnog oxytocine gestart wordt. Met behulp van EHG kan hier mogelijk een antwoord op gevonden worden. In deze observationele pilotstudy wordt met behulp van EHG de contractiefrequentie vergeleken voor en na starten van epidurale analgesie, waarbij een statistisch significante maar klinisch irrelevante kleine afname in contractiefrequentie gevonden wordt.

Hoofdstukken 3 en 4 Chronische postoperatieve pijn (chronic postsurgical pain, CPSP) na een keizersnede komt voor bij meer dan 10% van de patiënten en heeft een negatieve impact op het welbevinden van moeder en kind. Ernstige acute postoperatieve pijn laat een consistent verband zien met CPSP; spinale (intrathecale, [IT]) toevoeging van morfine aan spinale anesthesie geeft een langdurige postoperatieve acute pijnstilling. In **hoofdstuk 3** wordt er in een prospectieve dubbelblind gerandomiseerde placebo-gecontroleerde studie onderzocht of de toevoeging van langwerkende morfine aan het spinale anesthesie mengsel een vermindering van CPSP na 3 en 6 maanden laat zien. Zowel in de IT morfine groep als in de placebogroep wordt eventueel optredende acute postoperatieve pijn optimaal behandeld met behulp van een multimodaal analgesie regime, waarbij verschillende analgetica zorgen dat de acute postoperatieve pijn niet boven een NRS (numeric rating scale) pijnscore van 3 op de schaal van 10 uitkomt. Er wordt geen associatie gevonden tussen het gebruik van IT morfine en het optreden van CPSP. **Hoofdstuk 4** is een secundaire analyse van deze studie, waarin onderzocht is of er een associatie bestaat tussen postpartum depressie (PPD) en CPSP. Er wordt een significante associatie gevonden. Vrouwen met PPD symptomen ervoeren significant vaker CPSP, zonder dat er een directe of indirecte (via PPD) associatie gevonden werd tussen acute postoperatieve pijn en CPSP.

Hoofdstuk 5 is een tweede secundaire analyse van de intrathecale morfine studie uit hoofdstuk 3. In deze studie wordt onderzocht of een reeds tijdens de zwangerschap bestaande depressie van invloed is op het optreden van bloeddrukdaling tijdens het starten van spinale anesthesie voor een keizersnede. Depressie tijdens de zwangerschap heeft een negatieve invloed op het functioneren van het autonome zenuwstelsel dat onder andere verantwoordelijk is voor de regulatie van de bloeddruk onder alle omstandigheden. Patiënten met tekenen van antepartum depressie vertoonden statistisch significant meer postspinale hypotensie tijdens een electieve keizersnede.

Hoofdstuk 6 Postspinale hypotensie, de bloeddrukdaling die kan optreden na toediening van spinale anesthesie, kan op meerdere manieren voorkómen en behandeld worden. Een nauwkeurig gedoseerde hoeveelheid LA is de belangrijkste factor die de optimale balans tussen goede intra-operatieve anesthesie en het voorkomen van hypotensie bepaalt. Aanpassing van de dosering aan maternale lengte en/of gewicht draagt hieraan bij, maar het is onbekend of bestaande doseerschema's ook toepasbaar zijn op zwangere patiënten met een klein postuur (<150 cm). Deze prospectieve dubbelblind gerandomiseerde studie vergelijkt LA doseringen voor spinale anesthesie bij keizersnedes in Nepalese zwangeren van klein postuur, die ofwel bepaald wordt in relatie tot lengte alleen of in relatie tot lengte en gewicht. Er werd geen statistisch significant verschil gevonden tussen de beide groepen betreffende het optreden van postspinale hypotensie, maar patiënten met de iets hogere doseringen berekend aan de hand van lengte alleen, bleken wel significant minder vaak extra pijnstilling nodig te hebben tijdens de procedure.

Hoofdstukken 7-10, gecentreerd rondom de EPiMAP studie, hebben postdurale punctie hoofdpijn (PDPH) als onderwerp. PDPH kan het gevolg zijn van verschillende invasieve neuraxiale procedures en behandelingen, en is niet altijd te voorkomen. PDPH als gevolg van een accidentele durale punctie (ADP) bij het initiëren van epidurale pijnstilling tijdens de partus daarentegen is een ongewenste en iatrogene complicatie, die niet altijd spontaan binnen een paar dagen overgaat. Een van de weinig bewezen effectieve behandelingen van PDPH is een epidurale bloodpatch (EBP). Hierbij wordt 10-20 ml autoloog bloed in de epidurale ruimte geïnjecteerd waardoor de klachten meestal verminderen of helemaal verdwijnen. **Hoofdstuk 7** is een uitgebreid review van de bestaande kennis over PDPH, de onderliggende pathofysiologie, symptomatologie en de verschillende behandelopties. **Hoofdstuk 8** is het eerste artikel van de EPiMAP (European Practices in the Management of Accidental Dural Puncture in Obstetrics) studie, een prospectieve cohortstudie (1001 pts.) waarvoor patiënten geïncludeerd werden in de meeste Europese landen. EPiMAP beschrijft het beloop van PDPH na ADP tijdens het starten van epidurale pijnstilling gedurende de bevalling en de verschillende toegepaste behandelmethodes. Vergeleken met patiënten die alleen met conservatieve methodes behandeld werden, bleken patiënten die een EBP kregen vooraf ernstiger symptomen te hebben. **Hoofdstuk 9** bestudeert vervolgens de 643 EPiMAP patiënten die een EBP kregen en onderzocht de factoren geassocieerd met het slagen van deze behandeling. Bij slechts 33% van de patiënten verdwenen de klachten compleet, bij 38% gedeeltelijk, terwijl er bij 28% sprake was van een mislukte EBP, gedefinieerd als een NRS score ≥7 na de EBP, en/of het toepassen van een 2e EBP. Risicofactoren voor het falen van een EBP waren a. een korte tijdsduur tussen de ADP, verschijnen van PDPH symptomen en het toepassen van een EBP, b. een hoger lumbaal niveau van de oorspronkelijke ADP, en c. een voorgeschiedenis met migraine. **Hoofdstuk 10** gaat opnieuw in op de onderliggende mechanismes van PDPH, maar nu vanuit het perspectief van de diverse behandelingen waarvoor nog onvoldoende bewijs is, maar die wel lijken bij te dragen aan vermindering of verdwijning van de klachten.

Toekomstperspectieven

Obstetrische anesthesie is in Nederland een nauwelijks bekend onderdeel van de anesthesiologie, maar wereldwijd vormt het een voortdurend evoluerend vakgebied met veel klinisch-wetenschappelijk onderzoek dat bijdraagt aan een betere zorg voor onze zwangere patiënten. Helaas worden de onderliggende fysiologische mechanismes minder bestudeerd, terwijl deze vaak nog gebaseerd zijn op gedateerde veronderstellingen zoals bijvoorbeeld blijkt bij PDPH. Wetenschappelijke vooruitgang vraagt echter om meer dan alleen klinisch onderzoek: het vereist een hernieuwde focus op de onderliggende pathofysiologie en meer interdisciplinaire nieuwsgierigheid. De huidige grenzen van klinisch-wetenschappelijk onderzoek moeten vooral worden gezien als een uitnodiging om nieuwe hypotheses te formuleren, gebaseerd op de nieuwste basaal-wetenschappelijke bevindingen.

De unieke Nederlandse verloskunde wordt gekenmerkt door een fysiologische benadering van de bevalling met, vergeleken met andere landen, minder invasieve ingrepen. Deze nadruk op natuurlijke bevalling met minimale interventies, is echter onder vuur komen te liggen sinds 2008, toen bekend werd dat er vergeleken met de ons omringende landen een verhoogde perinatale mortaliteit bestond. Een stuurgroep werd opgericht waar uiteindelijk het College Perinatale Zorg (CPZ) uit voortkwam, en de Integrale Zorgstandaard Geboortezorg werd ontwikkeld. Deze initiatieven erkenden echter onvoldoende de bijdrage van anesthesiologie aan maternale veiligheid, ondanks dat anesthesiologen betrokken zijn bij ongeveer 40% van alle bevallingen. Er is een toenemende vraag naar pijnstilling gedurende de partus, en steeds vaker bestaat er co-morbiditeit waarvoor medisch ingrijpen noodzakelijk is. Terwijl in veel Europese landen de obstetrisch anesthesioloog een actieve rol heeft binnen de peripartum zorg, is er in Nederland te weinig samenwerking en ontbreekt het besef dat obstetrische anesthesiologie kan bijdragen aan een tijdiger en beter inspelen op verslechterende maternale omstandigheden.

Optimalisatie van klinische obstetrische zorg behoeft meer en betere participatie van anesthesiologen op de verloskundige werkvloer, een proactievere deelname aan multidisciplinair overleg en meer aandacht voor obstetrische anesthesiologie, niet alleen binnen de opleiding tot anesthesioloog maar ook binnen die tot verloskundige en gynaecoloog. Uitgebreide evaluatie van de kwaliteit van huidige anesthesiologische bijdrage en identificatie van structurele barrières voor optimalisatie zijn noodzakelijk: anesthesiologische vertegenwoordiging binnen beleidsorganisaties zoals het CPZ is essentieel.

Hoewel deze strategische inspanningen nog moeten worden geïnitieerd, is geleidelijke vooruitgang waarneembaar. Anesthesiologen dragen steeds meer bij aan de ontwikkeling van multidisciplinaire obstetrische richtlijnen, het eerste onderzoeksprogramma dat kwaliteit en uitkomstmaten bij keizersnede meet is opgezet, en scholingsmogelijkheden in obstetrische anesthesiologie breiden zich langzaam uit.

Alleen door werkelijke integratie van anesthesiologische expertise binnen het multidisciplinaire obstetrische zorgteam kunnen de benodigde kwaliteitsverbeteringen in obstetrische anesthesie worden bereikt. Dit vraagt niet alleen voortdurende toewijding van gespecialiseerde anesthesiegroepen en verhoogde steun van beroepsverenigingen, maar ook structurele, organisatorische hervormingen. Hierdoor kan tijdiger en betere anesthesiologische zorg geboden worden, hetgeen complicaties voorkomt, traumatische geboorte-ervaringen vermindert en een goede uitkomst voor moeder en kind bevordert.

De onderzoeken in dit proefschrift bieden bouwstenen voor de optimalisatie van obstetrische anesthesiologische zorg. Hoewel dergelijk klinisch wetenschappelijk onderzoek essentieel is om ons anesthesiologisch handelen te verbeteren, zijn genoemde organisatorische verbeteringen minstens zo belangrijk om uiteindelijk de kwaliteit van de anesthesiologische bijdrage aan de klinische geboortezorg te optimaliseren. Alleen door gelijktijdige vooruitgang van medisch inhoudelijk inzicht en multidisciplinaire samenwerking kunnen we streven naar een veiliger en effectievere obstetrische anesthesiologie voor alle vrouwen, ook in Nederland.

Appendices

List of abbreviations
Acknowledgements
Curriculum vitae

List of abbreviations

A

ADP	Accidental Dural Puncture
AICC	Akaike Information Criterion, Corrected
ANS	Autonomic Nervous System
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve

B

BIC	Bayesian Information Criterion
BMI	Body Mass Index
BPI	Brief Pain Inventory

C

CI	Confidence Interval
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CPSP	Chronic Postsurgical Pain
CSE	Combined Spinal-Epidural
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTG	Cardiotocogram/Cardiotocography
CPZ	College Perinatale Zorg
CVT	Cerebral Venous Thrombosis

E

EBP	Epidural Blood Patch
ECG	Electrocardiography
EDA	Epidural Analgesia
ED95	Effective Dose 95%
EHG	Electrohysterography
EPDS	Edinburgh Postnatal Depression Scale
EPiMAP	European Practices in the Management of Accidental Dural Puncture in Obstetrics
ERB	Ethical Review Board
ESAIC	European Society of Anaesthesiology and Intensive Care

F

FIGO	International Federation of Gynecology and Obstetrics

G

GONB	Greater Occipital Nerve Block

H

HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
HRV	Heart Rate Variability

I

ICB	Intracranial Bleeding
ICHD	International Classification of Headache Disorders
IQR	Interquartile Range
IRC	Institutional Review Committee
IT	Intrathecal
ITC	Intrathecal Catheter
IUPC	Intrauterine Pressure Catheter
IV	Intravenous

L

LA	Local Anesthetic/Anaesthetic
LEA	Labour Epidural Analgesia
LoR	Loss of Resistance

M

MRI	Magnetic Resonance Imaging

N

NFMS	Nemo Fetal Monitoring System
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

O

OAA	Obstetric Anaesthetists' Association
OIH	Opioid-Induced Hyperalgesia
ONSD	Optic Nerve Sheath Diameter
OR	Odds Ratio

P

PACU	Post-Anesthesia Care Unit
PCEA	Patient-Controlled Epidural Analgesia
PCS	Pain Catastrophizing Scale
PDPH	Postdural Puncture Headache
POTS	Postural Orthostatic Tachycardia Syndrome
PPD	Postpartum Depression
PRES	Posterior Reversible Encephalopathy Syndrome
PTSD	Post-Traumatic Stress Disorder

R

RCT	Randomized Controlled Trial

S

SA	Spinal Anesthesia
SAH	Subarachnoid Haemorrhage
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDH	Subdural Hematoma
SIH	Spontaneous Intracranial Hypotension
SNOSE	Sequentially Numbered, Opaque Sealed Envelopes
SPG	Sphenopalatine Ganglion
SPGB	Sphenopalatine Ganglion Block
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

T

TVS	Trigeminovascular System

V

VIF	Variance Inflation Factor

Acknowledgements

Obstetrische anesthesiologie (OA) is in Nederland vooralsnog een ondergewaardeerd subspecialisme. In mijn streven om dit te veranderen en de anesthesiologische zorg voor de (zieke) zwangere te verbeteren, ben ik geleidelijk een niet voor de hand liggende academische weg ingeslagen. Ik heb hierdoor het voorrecht gehad om vele interessante mensen te ontmoeten die elk op hun eigen wijze hebben bijgedragen aan mijn reis. Collega's die uitgroeiden tot vrienden, mentoren die nieuwe perspectieven openden, en medereizigers die momenten van twijfel omzetten in doorzetten. De collega's die me ingewijd hebben in obstetrisch anesthesiologisch onderzoek en de vrienden met wie ik nieuwe onderzoeksprojecten opgezet heb zijn geen van allen afkomstig uit de Nederlandse anesthesiologie. Dat er nu toch dit proefschrift ligt heb ik vooral te danken aan mijn hooggeschatte promotor en co-promotoren.

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Ook in Nederland en België zijn er vele collega's die deel uitmaken van de enthousiaste groep anesthesiologen en gynaecologen die optimale klinische samenwerking voor ogen hebben en die al dan niet actief binnen de sectie, SOBAN, NVOG en NVA bijdragen aan studies, projecten en noodzakelijk overleg. Te veel mensen om op te noemen, maar bij deze wil ik toch van de gelegenheid gebruik maken om een ieder te danken, jullie geven invulling aan de OA, waardoor deze zich nu in ons land langzaam, maar gestaag ontwikkelt tot een noodzakelijk en volwaardig subspecialisme. Beste Ingrid, Claire, Sarah en Anouk, voor jullie maak ik graag een uitzondering, als vrienden waren al die jaren plannen maken, frustraties delen en successen vieren zoveel leuker, superdank.

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Lieve Mario, Carlos, Oscar, Alexander en Felice. Lieve Genia Felice. Alles is uiteindelijk liefde. De kwetsbaarheid van ons bestaan is meestal verborgen, maar eenmaal ervaren, nooit ver weg te denken. Ook al beseffen jullie dit misschien niet, maar jullie, mijn gezin, vormde de basis van dit proefschrift en mijn dieptste drijfveer om ook dit project binnen de obstetrische anesthesiologie tot een goed einde te brengen. Een jaar met een gouden randje werd niet alleen een bron van inspiratie en hopelijk een bijdrage aan een veiliger geboortezorg, maar bracht jullie ook het nodige ongemak. Steeds vaker op reis, en steeds achter mijn bureau: dankzij jullie werd dit alles mogelijk, dit proefschrift is ook jullie succes. Ik beloof je Mario, vanaf nu wordt het niet meer steeds meer.

Curriculum Vitae

Name: Alexandra Marie-Jeanne Victoria Schyns-van den Berg (Xandra)
Place of birth: Valkenburg-Houthem, The Netherlands

Education

1970-1971: Edron Academy, Mexico D.F., Mexico
1971-1972: John F. Kennedyschool, Queretaro, Mexico
1973-1978: Coriovallum College, Heerlen, the Netherlands
1978-1979: Propedeuse Dutch Language and Literature, Utrecht University (NL)
1979-1987: University of Utrecht, Medical School, 1987 MD
2016-2017: Global Clinical Scholar Research Training (GCSRT), Harvard Medical School

Professional Appointments

1987-1989: Internship Cardiology, Leyenburg Hospital, Den Haag (NL)
1989-1995: Internship/Residency Anaesthesiology, University Medical Centre Utrecht (NL)
1995-1996: Chef de Clinique Anesthesiology, Hospital de Baronie, Breda (NL)
1996-2024: Consultant Anaesthesiologist, Albert Schweitzer Hospital, Dordrecht (NL)
2025-present: Locum Anesthesiologist, currently at Admiraal de Ruyter Hospital, Goes (NL)

Professional Activities

2007-2017: Board member and chair subcommittee Dutch Obstetric Anesthesiology (NVA)
2010-Present: Refresher Course Obstetric Anaesthesia (BE-NL) Organizer and co-director
2016-2018: 25th Anniversary Congress of Dutch Obstetric Anaesthesia, May 2, 2018 during the International Forum on Quality and Safety in Healthcare (IFQSH) “Facilitating Collaboration, Improving Care: Anaesthesia’s Role in Safe Obstetrics” Amsterdam (NL), chair of organizing committee
2017-2024: Obstetrische Anesthesie Foundation, chair of board
2022: Organisation and provision of an online course on Obstetric Anaesthesia, with assistance of many international experts, aimed at residents of Myanmar and neighbouring countries who lack formal training

Editorial Activities

2017: Co-editor Anesthesie en de normale zwangerschap (ACCO)
2024: Co-editor Anesthesiologie en Zwangerschap (ACCO)
2023-2025: Contributor to e-learning: Obesitas & Zwangerschap

Research Activities

2014-Present: EPiMAP (Epidural Practices in the Management of Accidental Dural Puncture in Obstetrics, ESA Clinical Trial Network), member of the Steering Committee. (Chief Investigator Dr. Anil Gupta, Karolinska Institute, Stockholm, Sweden)
2017-2021: Co-investigator IT morphine: Effect of IT Morphine on Chronic pain after elective CS. (Chief Investigator Dr. Asish Subedi, Koirala Institute, Dharan, Nepal)
2022-present: Co-investigator: Effect of altitude on postdural puncture headache after Caesarean Section (Chief Investigator Dr. Asish Subedi, Koirala Institute Dharan, Nepal)
2019-2022: Co-investigator Survey Obstetric Anesthesia in the Netherlands
2017-2025: Steering Committee member MaCriCare (Maternal Critical Care in Europe)
2020-2024: Co-investigator Neuraxial analgesia: interaction with progression of labour Maxima Medical Centre, Veldhoven
2025-present: PreMaCare: Prospective studies in Maternal Care, Cracow (Poland)
2024-present: Preparing a registry of Neuraxial procedures & patient follow-up, Stockholm (SE)

PUBLICATIONS

(* included in this thesis)

A&I, 2010 Pijnbestrijding gedurende de partus M. Coppens, *A.M.J.V. Schyns-van den Berg*

Medisch Contact, 16 Dec. 2010 Partus en pijn hoeven nergens hand in hand *A.M.J.V. Schyns-van den Berg*, N.M.A.A. Engel, M.A.E. Marcus, I.C.M. Beenakkers

Current Opinion in Anaesthesiology 28 (3): 267-74 (2015) Postcaesarean section analgesia: are opioids still required? *Schyns-van den Berg AM,* Huisjes A, Stolker RJ

European Journal of Anaesthesiology, 35: 553-555 (2018) Anaesthesiology and ethics: Autonomy in childbirth *Alexandra M.J.V. Schyns-van den Berg*, Frederique Claudot, Antoine Baumann

European Journal of Anaesthesiology 36 (12): 973-976 (2019) Skin-to-skin contact during caesarean delivery: an intriguing interaction between the mother and her child Nicolas Brogly, Leonie Slegers, *Alexandra Schyns-van den Berg*, Emilia Guasch

***British Journal of Anaesthesia, 125 (6): 1045-1055 (2020)** Management practices for postdural puncture headache in obstetrics: a prospective, international, cohort study Anil Gupta, Christian von Heymann, Anders Magnuson, Seppo Alahuhta, Roshan Fernando, Marc Van de Velde, Frederic J. Mercier, *Alexandra M. J. V. Schyns-van den Berg*

Protocolos asistenciales de la sección de anestesia obstétrica de la SEDAR (2021) Chapter 9: Recomendaciones anestésicas en los partos de bajo riesgo Alexandra Schyns-van den Berg

***British Journal of Anaesthesia 128 (4): 700-707 (2022)** Intrathecal morphine does not prevent chronic postsurgical pain after elective Caesarean delivery: a randomised controlled trial Asish Subedi, *Alexandra M. J. V. Schyns-van den Berg*, Parineeta Thapa, Prakash M. Limbu, Yojan Trikhatri, Anjali Poudel, Yogesh Dhakal and Sabin Bhandari

***British Journal of Anaesthesia, 129 (5): 758-766 (2022)** Factors associated with failed epidural blood patch after accidental dural puncture in obstetrics: a prospective, multicentre, international cohort study Anil Gupta, Marc Van de Velde, Anders Magnuson, Christian von Heymann, Emilia Guasch, Seppo Alahuhta, Frederic J. Mercier, *Alexandra M. J. V. Schyns-van den Berg*

***Best Practice & Research Clinical Anaesthesiology, Volume 37, Issue 2, June 2023, 171-187** Postdural puncture headache revisited *Schyns-van den Berg AMJV*, Gupta A

***Journal of Anesthesia 2023 Dec; 37(6): 905-913** Effect of height versus height/weight-based spinal bupivacaine on maternal hemodynamics for elective cesarean in short stature patients: a randomized clinical trial Asish Subedi, Parineeta Thapa, Rajesh Prajapati, *Alexandra M.J.V. Schyns-van den Berg*

Ultrasound in Obstetrics and Gynecology, 62(5), 753-754. 2023 Can national registry data be used to assess effects of epidural analgesia during labor? Papazova, D. A., *Schyns-van den Berg, A. M. J. V.*, Beenakkers, I. C. M., & van den Bosch, O. F. C.

Ultrasound in Obstetrics and Gynecology, 62(5), 755-757 2023 Epidural analgesia and emergency delivery: exploring causal misconceptions. van den Bosch, O. F. C., Beenakkers, I. C. M., Boonstra, L., Papazova, D. A., & *Schyns-van den Berg, A. M. J. V.*

Anaesthesia Critical Care & Pain Medicine, Volume 43, Issue 3, 2024 Preparedness for severe maternal morbidity in European hospitals: The MaCriCare study. Krawczyk, P., Dabrowska, D., Guasch, E., Jörnvall, H., Lucas, N., Mercier, F. J., *Schyns-van den Berg, A.M.J.V.*, Weiniger, C. F., Balcerzak, Ł., & Cantellow, S.

Anaesthesia Critical Care & Pain Medicine, Volume 43, Issue 4, 2024 Obstetric units' preparedness to manage critically ill women. The second report from the MaCriCare study. Krawczyk, P., Dabrowska, D., Guasch, E., Jörnvall, H., Lucas, N., Mercier, F. J., *Schyns-van den Berg, A.M.J.V.,* Weiniger, C. F., Balcerzak, Ł., & Cantellow, S.

***Best Practice & Research Clinical Anesthesiology, Volume 38, Issue 2, June 2024, 267-277** Postdural puncture headache: Beyond the evidence *A.M.J.V. Schyns-van den Berg*, D.N. Lucas, L. R. Leffert

***International Journal of Obstetric Anesthesia, 2025 May; 62: 104296** Uterine contraction frequency after initiation of labour epidural analgesia using electrohysterography monitoring: a prospective pilot study Frenken MWE, *Schyns-van den Berg AMJV*, Oei SG, Regis M, Meijer P, Houthoff-Khemlani K, van Laar JOEH, van der Woude DAA

***Biopsychosocial Science and Medicine, 87(5):349-352, June 2025** Preoperative higher depression scores are associated with risk of hypotension following spinal anesthesia for caesarean delivery Subedi, Asish; Thapa, Parineeta; *Schyns-van den Berg, Alexandra M.J.V.*

International Journal of Obstetric Anesthesia, accepted July 16, 2025 Maternal experience in the intensive care unit and Post-discharge care: the third report from the MaCriCare study S. Cantellow, Ł. Balcerzak, *A.Schyns-van den Berg*, D. Dabrowska, E. Guasch, H. Jörnvall, N. Lucas, F.J. Mercier, C.F. Weiniger, P. Krawczyk, the MaCriCare Study Group

***Canadian Journal of Anesthesia, published online July 22, 2025** Association between postpartum depression and chronic postsurgical pain after Cesarean delivery: a secondary analysis of a randomized trial Asish Subedi, Sharon Orbach-Zinger, *Alexandra M.J.V. Schyns-van den Berg*

Regional Anesthesia & Pain Medicine, accepted August 2025 Voluntary Registry-Based Analysis of Risk Factors for Accidental Dural Puncture in Epidural Anesthesia Jörnvall, Henrik; Orbach-Zinger, Sharon; Schyns-van den Berg, Alexandra

LECTURES & ORAL PRESENTATIONS

2021

- Royal Society of Medicine (23-07-2021): Dutch Obstetric Care, the best of 2 worlds?
- ESRA Virtual Conference (09-09-2021): PDPH: New strategies for an old problem
- DARA-ESRA Radboud MC: What's new in obstetric anesthesia
- AIOS-dag (06-11-2021): Problem-based learning discussion: Obesitas & COVID-2019
- RCOA (15-11-2021): Sepsis in de zwangerschap en het kraambed

2022

- Myanmar Residents Virtual Lectures (January-March 2022): 7 sessions of 2 hours each
- International Congress on Ambulatory Surgery, Bruges (31-05-2022): Caesarean section in day surgery?
- Euroanaesthesia Milano:
  - (04-06-2022) The obese patient in the labour ward, intrapartum analgesia
  - (06-06-2022) Primum non nocere, so why do postdural puncture headaches occur frequently in labouring women?
- ESRA Thessaloniki:
  - The Obstetric patient with pre-existing neurologic disease, can she have an epidural?
  - How to manage pain during anesthesia for c-section?
- OAA 3-day course, London (09-11-2022): PDPH, new perspectives
- New York PGA (12-12-2022): Clinical Trial Network of the ESAIC: the concept works, EPiMAP

2023

- ESRA/OAA online (20-01-2023): Neuraxial anesthesia for Caesarean Section
- Wintersymposium Leuven (10-02-2023): The placenta and uteroplacental perfusion: the essentials!
- RCoA Anaesthetic Updates, virtual (28-03-2023): Managing patients requiring emergency C-section
- 2nd Summer School of OA, Banja Luka, virtual (10-06-2023): EPiMAP study results
- ESRA World Congress on Regional Anesthesia, Paris (08-09-2023): Managing PDPH in obstetric neuraxial anesthesia
- Monothematic Meeting Obstetric Anesthesia, Algarve:
  - (02-10-2023) A history of obstetric Anesthesia
  - (05-10-2023) Anesthetic management of neurologic disease in pregnancy
  - (06-10-2023) PDPH
  - Avoiding medicolegal problems in obstetric anesthesia
- Association of Obstetric Anesthesiologists of Ukraine, Kyiv, Virtual:

  - Anesthetic management of neurologic disease in pregnancy
  - Postdural puncture headache, current insights, improved management
- OAA London (22-11-2023): PDPH: Managing complications or preventing them?
- Slovenian Society of Obstetric Anesthesiology, Ljubljana (18-11-2023): PDPH, prevention and treatment
- RCOA Leuven (04-12-2023): PDPH, een update

2024

- ESRA webinar (April 2024): PDPH
- SOAP Denver, USA (05-05-2024): PDPH, beyond the guidelines
- 3rd Summer School of Obstetric Anesthesia, Banja Luka (08-06-2024): Catching waves, studying the effect of neuraxial labour analgesia on labor and delivery
- Israeli Society of OA, Jerusalem (14-06-2024): Interesting hot topics in obstetric anesthesia: PDPH
- SSAI Oulo, Finland (20-06-2024): PDPH and its long-term consequences
- ESRA Prague:
  - Cardiac arrest in pregnancy
  - Defining the walking epidural
- Philippine Society of Anesthesiology Annual Convention, Manila (27-11-2024):
  - Catching Waves: Electrohysterography to Study the Effects of Neuraxial Analgesia on Progress of Labour
  - Neurologic disease in pregnancy
- Slovenian Society of Obstetric Anesthesiology, Ljubljana (30-11-2024): The walking Epidural

2025

- World Day Regional Anesthesia, Veenendaal (25-01-2025): Obstetric RA: Evidence-based practice
- POIDA, Rotterdam (19-04-2025): Spinaal, epiduraal, CSE - wat te doen bij complicaties
- 4th Summer School of Obstetric Anesthesia, Banja Luka (06-06-2025): Epidural analgesia: the good, the bad, the ugly?
- Amsterdam Spontaneous Intracranial Hypotension Symposium (SIH) (29-06-2025): The basis of PDPH