

Remifentanil for labour pain : safety and efficacy Douma, M.R.

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Chapter 1

General introduction

Most women describe the pain of childbirth as one of the most intense forms of pain that can be experienced during their life, although the intensity of pain parturients experience during labour can vary.^{1,2}

Pain during the first stage of labour is mainly visceral in nature and arises from the uterus and cervix. It is the result of dilatation of the cervix and distension of the lower uterine segment during contractions.³ The pain is transmitted via spinal nerves T10 through L1. During the second stage of labour, when the cervix is fully dilated, pain occurs from stretching and tearing of tissues of vagina, perineum and pelvic floor. This somatic pain is transmitted via the pudendal nerve, entering the spinal cord via nerve routs S2-S4.⁴

Throughout history, treating labour pain has been a controversial topic. The oldest form of pain relief and still in use today is opium. Opium was discovered around 3400 BC. In the 19th century, separation of active components of opium became possible and its principle ingredient morphine could be isolated. In 1847, the Scottish obstetrician James Young Simpson was the first person administering chloroform and ether as labour analgesic. Although many considered labour analgesia unnatural, against religious beliefs and probably harmful, it rapidly became popular. Even Queen Victoria used chloroform during the birth of Prince Leopold (1853). In the early 1900s nitrous oxide, originally discovered in 1799 by Davis, an English chemist, was being used as labour analgesic. In the 1940s neuraxial analgesia during labour was introduced by John Bonica, an American anesthesiologist. His wife was one of the first women to receive an epidural for the birth of their child.⁵ In 1947, John Bonica, at that time head of the department of Anesthesiology at Tacoma Hospital, organised one of the first round-the-clock labour analgesia services. From 1960 on, when Bonica was chairman of the department of Anesthesiology of University of Washington, caudal analgesia became the primary technique for treating labour pain.⁶

Today, there are several options to reduce labour pain, including both nonpharmacological and pharmacological methods. Non-pharmacological methods include (self-) hypnosis, sterile water injections, water immersion (pool or bath), aromatherapy, relaxation techniques (yoga/mediation), acupuncture/acupressure and transcutaneous electrical nerve stimulation (TENS). The aim of non-pharmacological options is primarily to help cope with the pain, whereas pharmacological methods aim to relieve the pain of labour.⁴ Pharmacological interventions include inhaled analgesia, opioids, local anesthetic nerve blocks and neuraxial analgesia. Of inhaled analgesia, nitrous oxide (in 50% oxygen) is used in obstetric analgesic practice. Advantages of the technique are easy administration, absence of effect on uterine contractions, minimal effect on maternal hemodynamic parameters and a rapid onset and offset of action. Nitrous oxide is widely administered in the United Kingdom and Scandinavia. The use of nitrous oxide in the Netherlands has declined considerably since the introduction of strict occupational exposure limits. These limits were introduced because epidemiologic studies showed increased reproductive risks (e.g. miscarriage, congenital anomalies and reduced rates of fertility) for health professionals who were frequently exposed to nitrous oxide.⁷ With the advent of new scavenging systems, the use of nitrous oxide has regained some popularity.

Opioids are relatively inexpensive and easy to administer. Parental and intramuscular administered opioids during labour include morphine, nalbuphine and fentanyl. The most commonly used systemic opioid is pethidine, although its efficacy is being challenged for some time now.⁸⁻¹⁰ In general, up to two-thirds of women who receive opioids during labour report only poor or moderate pain relief. Moreover, opioid drugs are associated with maternal nausea, sedation and drowsiness.¹¹ For the neonate, respiratory depression can occur.

Of the local anesthetic nerve blocks, pudendal and paracervical nerve blocks are most commonly used in obstetrics. A pudendal block can be performed during the second stage of labour by injection of a local anesthetic around the trunk of the pudendal nerve.⁴

Epidural analgesia is a central nerve blockade technique, which involves the injection of a local anesthetic, with or without an opioid, into the lower region of the spine close to the nerves that transmit painful stimuli from the contracting uterus and birth canal.¹² It is proven to provide effective pain relief during labour. Possible maternal side effects include hypotension, pruritus, an increase in temperature and urinary retention. A Cochrane review, published in 2011, concluded epidural analgesia was associated with increased risk of instrumental delivery.¹² Among the pharmacological methods of pain relief, epidural analgesia is considered to be the most effective form or 'gold standard'. Nevertheless, even in the developed world, epidural analgesia is not always available to all parturients. This can have several reasons. There can be an absolute or relative contra-indication to the use of central neuraxial analgesia or it is possible that labour progresses too rapidly. There can be logistic problems, as an anesthesiologist is required to perform the procedure. Therefore, there is need for other effective obstetric analgesics to provide an alternative.

Chapter 1

Remifentanil is a synthetic opioid with direct agonist action specifically at the µ-opioid receptor. It has been developed for usage during general anesthesia under conditions of strict monitoring and is further used for deep sedation, again under conditions of strict monitoring. The opioid became FDA approved in 1996 and the first case report on use of remifentanil as labour analgesic appeared in 1999.¹³ Over the last 15 years remifentanil patient-controlled analgesia (PCA) has become an increasingly popular labour analgesic, however, the opioid is not officially registered for obstetric analgesic use. Remifentanil has an unique pharmacokinetic profile with a short terminal half-life due to hydrolysis by non-specific blood and tissue esterases and consequently a metabolism independent of renal and/or kidney function. It has a rapid onset of action and short latency to its peak effect, which makes it very suitable for PCA.¹⁴ Remifentanil crosses the placenta, but is rapidly metabolized and/or redistributed by the fetus.¹⁵ Adverse effects resemble those of other potent opioid analgesics and include respiratory depression with oxygen desaturation and sedation.¹⁶ ¹⁷

The aim of this thesis was to evaluate the efficacy and safety of remifentanil in its treatment of labour pain.

In chapter 2 a randomised controlled trial is performed comparing the analgesic efficacy of remifentanil to pethidine and fentanyl, in a patient controlled setting.

In chapter 3 remifentanil PCA is compared to epidural analgesia with respect to analgesic efficacy in a randomised controlled study.

Chapter 4 describes a randomised controlled trial comparing side effects of remifentanil PCA and epidural analgesia.

In Chapter 5 pharmacokinetic pharmacodynamic modelling and simulation studies are presented, using data from a previous study on the effect of iv remifentanil on ventilation in healthy volunteers. We aimed to better understand the effect of remifentanil PCA during labour on ventilation, rather than on surrogate markers of ventilation such as oxygen saturation.

In Chapter 6 a systematic review is performed on data from trials on side effects of remifentanil and other labour analgesics.

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Chapter