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Epidural analgesia and emergency delivery for presumed fetal compromise: *post-hoc* analysis of RAVEL multicenter randomized controlled trial

E. S. E. TABERNÉE HEIJTMEIJER[1], H. GROEN[2], S. E. DAMHUIS[1,3], L. M. FREEMAN[4], J. M. MIDDELDORP[5], W. GANZEVOORT[3,6] and S. J. GORDIJN[1]

[1]*Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;* [2]*Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;* [3]*Department of Obstetrics and Gynecology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands;* [4]*Department of Obstetrics and Gynecology, Leiden University Medical Center, Leiden, The Netherlands;* [5]*Department of Obstetrics and Gynecology, Ikazia Hospital, Rotterdam, The Netherlands;* [6]*Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands*

KEYWORDS: epidural analgesia; fetal compromise; fetal growth restriction; FGR; intrapartum; labor; patient-controlled analgesia; placental insufficiency; remifentanil; SGA; small-for-gestational age

CONTRIBUTION

What are the novel findings of this work?
Intrapartum epidural analgesia is associated with a higher risk of emergency delivery for presumed fetal compromise compared with patient-controlled remifentanil. The highest rate of emergency delivery was observed in those with the lowest birth-weight quintile.

What are the clinical implications of this work?
Given that epidural analgesia is the most effective method of pain relief during labor, the implications of our findings remain unclear. However, given the lack of other relevant data and that pain perception is influenced by emotion and motivation, informing women of the potential risk of presumed fetal compromise associated with epidural analgesia may lead to exploration of alternative pain relief methods.

ABSTRACT

Objective *To investigate the association between epidural analgesia (EDA)* vs *patient-controlled remifentanil analgesia (PCRA) and emergency delivery for presumed fetal compromise, in relation to birth-weight quintile.*

Methods *This was a* post-hoc *per-protocol analysis of the RAVEL multicenter equivalence randomized controlled trial. Non-anomalous singleton pregnancies between 36 + 0 and 42 + 6 weeks' gestation were randomized at the time of requesting pain relief to receive EDA or PCRA. The primary outcome was emergency delivery for presumed fetal compromise. Secondary outcomes included mode of delivery and neonatal outcomes. Analysis was performed according to birth-weight quintile and was corrected for relevant confounding variables.*

Results *Of 619 pregnant women, 336 received PCRA and 283 received EDA. Among women receiving EDA, 14.8% had an emergency delivery for presumed fetal compromise, compared with 8.3% of women who received PCRA. After adjusting for parity, women receiving EDA had higher odds of presumed fetal compromise compared to those receiving PCRA (odds ratio, 1.69 (95% CI, 1.01–2.83)). A statistically significant linear-by-linear association was observed between presumed fetal compromise and birth-weight quintile (*P = *0.003). The incidence of emergency delivery for presumed fetal compromise was highest in women receiving EDA and delivering a neonate with a birth weight in the lowest quintile.*

Conclusions *Intrapartum EDA is associated with a higher rate of emergency delivery for presumed fetal compromise compared to treatment with PCRA. Birth-weight quintile is a strong predictor of this outcome, independent of pain management method. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

Correspondence to: Dr S. J. Gordijn, Department of Obstetrics and Gynecology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands (e-mail: s.j.gordijn@umcg.nl)

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INTRODUCTION

Labor pain is considered to be one of the most severe forms of pain in a woman's life[1]. Epidural analgesia (EDA) is the most effective method of pain relief during labor[2], and is recommended by the World Health Organization[3]. In The Netherlands, the use of EDA during labor rose[4,5] from 11.3% in 2008 to 23% in 2020.

A Cochrane systematic review and meta-analysis demonstrated that EDA is associated with a higher rate of instrumental vaginal delivery compared with opioids[2]. However, the reasons for this elevated rate have not been described and analyzed adequately.

A nationwide retrospective cohort study of all non-anomalous singleton term pregnancies with cephalic presentation recorded in The Netherlands perinatal registry between 1 January 2014 and 31 December 2018 showed that the risk of emergency delivery specifically for presumed fetal compromise was higher in women who received intrapartum EDA, compared with those who received no analgesia and alternative analgesia, and that the risk might be exacerbated at lower birth-weight centiles[6]. Considering that the smaller the fetus, the greater the chance of problems associated with reduced placental function[7], this finding suggests that the background risk of fetal compromise is related to placental reserve capacity. The suspected pathophysiological mechanism is that placental function is disturbed by a reduction in maternal blood pressure, a common side effect of EDA[8], which may result in decreased uteroplacental perfusion[9]. Consequently, fetuses already challenged by placental dysfunction may experience fetal hypoxia. Because of inherent flaws and biases in large retrospective databases, an analysis of prospective data would add strength to this hypothesis.

The RAVEL study was a Dutch randomized controlled trial that compared patient satisfaction between women that received patient-controlled remifentanil analgesia (PCRA) and those that received EDA[10]. In the intention-to-treat analysis, EDA was found to be superior to PCRA. However, crossover effects and a lack of subgroup exploration may have obscured the side effects of EDA.

Therefore, we conducted a per-protocol analysis of delivery data from the RAVEL study in order to support the hypothesis that EDA-induced fetal compromise results from disturbed placental function, by describing the association of EDA with the rate of emergency delivery for presumed fetal compromise in relation to the association with birth-weight quintile.

METHODS

The RAVEL study (NTR2551) was a multicenter randomized controlled equivalence trial conducted between 30 May 2011 and 24 October 2012 in 15 centers in The Netherlands, in which 1414 consenting women were randomized to PCRA or EDA during pregnancy before the onset of active labor[10]. The methods have been described extensively in the original manuscript and published study protocol[10,11]. In short, pregnant women were included if aged 18 years or older, were healthy or had mild systemic disease (American Society of Anesthesiologists (ASA) physical status classification 1 or 2)[12] and were scheduled to deliver vaginally after 32 weeks of gestation. As pain relief during labor was administered only upon request, not all women received analgesia. Analysis was performed on an intention-to-treat basis and crossover was recorded.

The current study was a *post-hoc* per-protocol analysis of original raw data from the RAVEL study. Inclusion criteria were singleton non-anomalous pregnancies with a term/near-term gestation (36 + 0 to 42 + 6 weeks). Women who were allocated to and received EDA, and those who were allocated to and received PRCA, were included. Women were excluded from analysis if they received a different treatment from that which they were allocated after randomization (crossover), used other types of pain relief or used no pain relief. This research falls within the scope of the medical ethics board of the RAVEL study (approval number p10-240) and written informed consent obtained at the time of participation in the RAVEL study covers the present research question.

Baseline characteristics included maternal age, race, gestational age at delivery, ASA physical status classification, parity, body mass index, previous Cesarean section, disease, medication use and onset of labor. The primary outcome was emergency delivery for presumed fetal compromise, which was defined as ventouse delivery, forceps delivery or Cesarean section for presumed fetal compromise, including cases in which the indication for emergency delivery was presumed fetal compromise in combination with obstructed labor. Secondary outcomes were instrumental or Cesarean section for obstructed labor only and for presumed fetal compromise only, delivery outcomes (mode of delivery (with reasons for intervention), postpartum hemorrhage, meconium-stained amniotic fluid, episiotomy, perineal rupture and hospital admission of mother and/or neonate) and neonatal outcomes (infant sex, birth weight, 5-min Apgar score < 7, umbilical artery pH < 7.10 and neonatal mortality). Birth-weight quintiles were calculated from Dutch Hoftiezer population reference charts[13].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 or 28.0 (IBM Corp., Armonk, NY, USA). The graph was generated with GraphPad Prism version 9.5 (GraphPad Software, San Diego, CA, USA). Given that the aim of the study was to elucidate the mechanism behind presumed fetal compromise, data were analyzed on a per-protocol basis. Patients who crossed over between treatment arms were not included in the primary analysis, but were evaluated separately in a secondary analysis. A subgroup analysis of women with

spontaneous onset of labor was performed. Patients with missing data were excluded on a per-analysis basis.

The effect of birth-weight quintile on the risk of emergency delivery for presumed fetal compromise was analyzed using linear-by-linear association in a two-by-five cross table. Logistic regression was performed to assess the effect on risk of presumed fetal compromise of EDA *vs* PCRA, birth-weight quintile and their interaction. We also analyzed data for possible confounding. Variables that changed the odds ratio (OR) between EDA and PCRA of presumed fetal compromise by more than 10% were considered relevant confounders.

Continuous data were compared using the independent samples *t*-test. Levene's test was used to check if the data were normally distributed. For categorical data, the chi-square test was used. The threshold for statistical significance was set at $P < 0.05$. Baseline characteristics and outcomes are presented using descriptive statistics. Because the participants of the RAVEL study were subjected to additional selection criteria for this study, characteristics and outcomes were compared between groups for significance. Missing data were declared if the prevalence exceeded 0.5%.

RESULTS

The RAVEL study database contained data from 1358 pregnant women. We excluded women who received no pain relief ($n = 564$), those with multiple pregnancy ($n = 21$), those who crossed over between treatment arms ($n = 58$), those who received another type of opioid pain relief ($n = 22$) and those who underwent change of primary treatment ($n = 74$) (Figure 1). This resulted in 619 women available for analysis, of whom 283 received EDA and 336 received PCRA.

Four baseline characteristics, namely race, heparin use, parity and incidence of hypertensive disorders of pregnancy (pre-eclampsia, pregnancy-induced hypertension

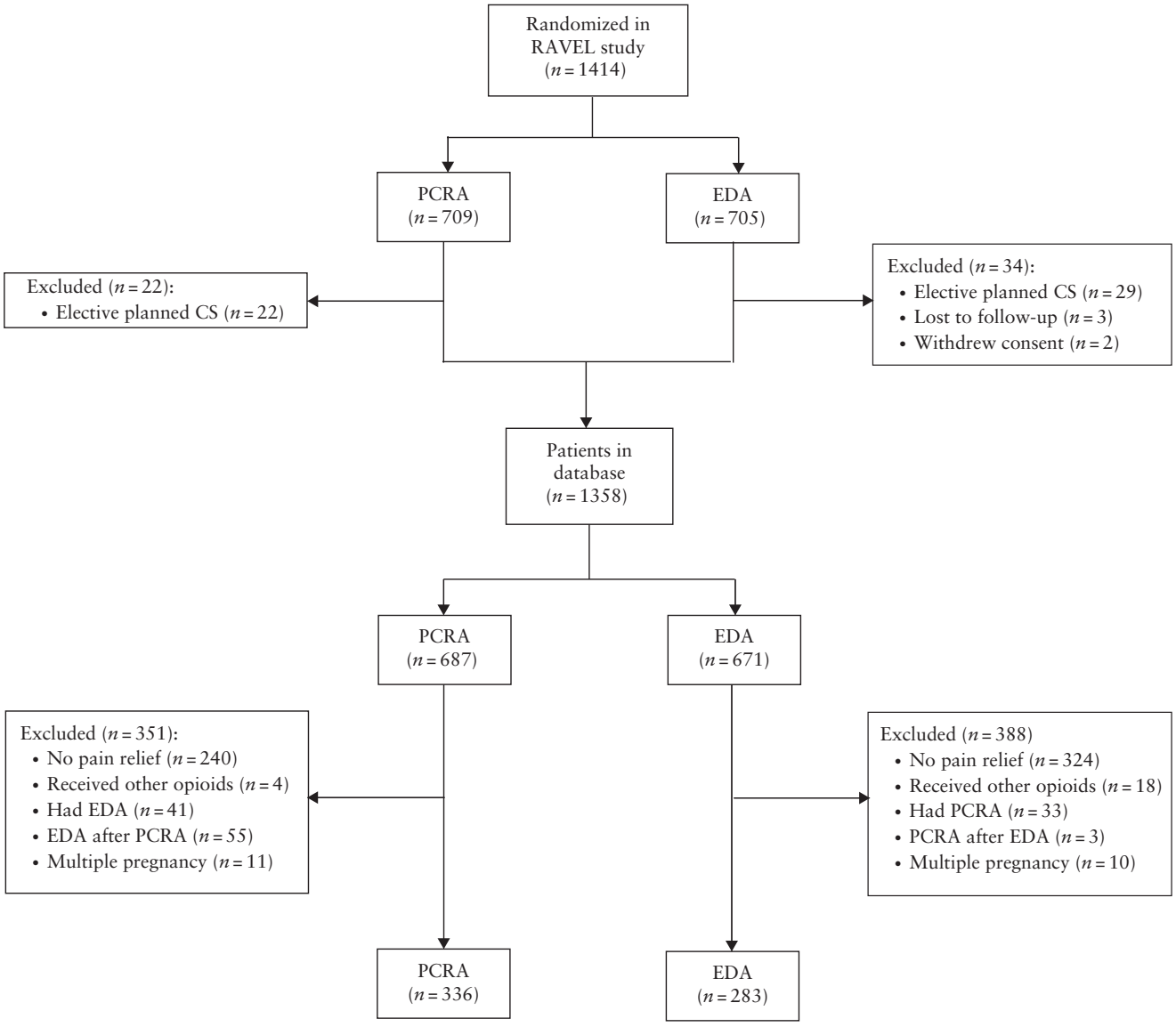

Figure 1 Flowchart summarizing randomization and flow of pregnant women in RAVEL study, according to allocation to patient-controlled remifentanil (PCRA) or epidural analgesia (EDA) in labor. CS, Cesarean section.

and HELLP syndrome), differed significantly between women who received EDA and those who received PCRA (Table 1). On logistic regression analysis, only parity showed relevant confounding of the effect of EDA *vs* PCRA on the risk of presumed fetal compromise. Mothers receiving EDA had higher odds of emergency delivery for presumed fetal compromise compared with those who received PCRA (OR, 1.69 (95% CI, 1.01–2.83)), corrected for parity. Of women receiving EDA, 14.8% had an emergency delivery for presumed fetal compromise, compared with 8.3% of women who received PCRA ($P = 0.011$) (Table 2). Umbilical artery pH < 7.10, when tested, was seen more often in the group receiving EDA compared with those receiving PCRA (7.5% *vs* 3.9%; $P = 0.021$).

A statistically significant linear-by-linear association was observed between risk of presumed fetal compromise and birth-weight quintile ($P = 0.003$). The interaction term of birth-weight quintile and EDA *vs* PCRA was not significant ($P = 0.92$). The rate of emergency delivery for presumed fetal compromise was highest in women who received EDA and delivered a neonate with a birth weight in the lowest quintile (Figure 2).

In the subgroup analysis of women with spontaneous onset of labor, the findings were similar. The rate of Cesarean section or instrumental delivery for obstructed labor only was 15.5% among women who received EDA and 14.0% among women who received PCRA. The rate of emergency delivery for presumed fetal compromise only was 8.4% among women who received EDA and 3.9% among women who received PCRA.

Table 1 Baseline characteristics of women in RAVEL study who received epidural analgesia (EDA) or patient-controlled remifentanil analgesia (PCRA), as allocated at randomization

Characteristic	*EDA (n = 283)*	*PCRA (n = 336)*	P
Maternal age (years)	31.3 ± 5.3	31.4 ± 5.3	0.770
Race			0.045
Caucasian	86.6	84.8	
Other	12.7	14.9	
Unknown	0.7	0.3	
GA at delivery (weeks)	39+2±2+2	39+5±1+2	0.362
ASA classification*			0.443
1	68.9	71.7	
2	31.1	28.3	
Parity			0.004
0	60.1	45.5	
≥ 1	39.9	54.5	
Body mass index (kg/m^2)	25.7 ± 4.8	25.2 ± 4.5	0.166
Previous CS	19.8	18.8	0.536
HDP	17.7	11.0	0.018
SGA	3.5	4.5	0.558
Systemic disease†			
Chronic hypertension	4.7	3.6	0.511
Psychiatric disease	3.2	2.4	0.537
Pulmonary disease	2.2	3.3	0.387
Vascular disease	0.0	0.6	0.195
Heart disease	0.7	1.2	0.545
Other	12.5	13.5	0.723
Medication‡			
Anticonvulsant	0.7	0.3	0.464
Antidepressant	1.8	2.1	0.778
Heparin	0.0	1.5	0.040
Aspirin	1.4	1.2	0.805
COPD	2.1	2.1	0.972
Antihypertensive	4.3	4.2	0.960
Other	12.9	11.4	0.584
Onset of labor			0.586
Spontaneous	32.2	34.2	
Induction	67.8	65.8	
AROM	39.2	39.3	0.604
Medication			0.399
PGE2 (Prostin, Propess®)	8.5	6.5	
PGE1 (misoprostol)	14.1	12.8	
Oxytocin	32.9	32.4	
Foley catheter	23.7	18.8	

Data are given as mean ± SD or %. *Physical status classification system of American Society of Anesthesiologists (ASA)[12]. †Data missing for 1.4% of women in EDA arm and 0.9% in PCRA arm. ‡Data missing for 1.1% of women in EDA arm. AROM, artificial rupture of membranes; COPD, chronic obstructive pulmonary disease; CS, Cesarean section; GA, gestational age; HDP, hypertensive disorder of pregnancy (pre-eclampsia, pregnancy-induced hypertension or HELLP syndrome); PGE1, prostaglandin E1; PGE2, prostaglandin E2; SGA, small-for-gestational age.

Table 2 Delivery and neonatal outcomes of pregnancies in RAVEL study that received epidural analgesia (EDA) or patient-controlled remifentanil analgesia (PCRA), as allocated at randomization

Outcome	*EDA (n = 283)*	*PCRA (n = 336)*	P
Delivery			
Emergency delivery for presumed fetal compromise	14.8	8.3	0.011
Mode of delivery			0.096
Spontaneous	67.8	75.9	
Vacuum/forceps extraction	14.5	9.8	
CS	16.3	14.0	
CS after vacuum/forceps	1.4	0.3	
PPH (> 1 L)	6.4	7.1	0.700
Meconium-stained AF	1.8	1.8	0.986
Perineal laceration			0.677
Rupture only	40.3	36.9	
Episiotomy only	27.9	27.1	
Rupture and episiotomy	1.8	1.5	
No laceration	30.0	34.5	
Admission			0.093
Neonatal only	1.4	1.8	
Maternal only	11.3	7.4	
Maternal and neonatal	58.3	53.3	
None*	29.0	37.5	
Neonatal			
Female sex	48.8	46.7	0.613
Birth weight (g)	3442 ± 505	3494 ± 523	0.249
Severe SGA†	6.0	4.8	
Mild SGA‡	6.0	8.3	
5-min Apgar score < 7	2.5	2.1	0.745
Umbilical artery pH tested	80.6	74.4	0.069
Umbilical artery pH < 7.10	7.5	3.9	0.021
Mortality	0.0	0.6	0.194

Data are given as % or mean ± SD. *Within 12 h of delivery. †Birth weight < 3rd centile. ‡Birth weight between 3rd and 10th centiles. AF, amniotic fluid; CS, Cesarean section; PPH, postpartum hemorrhage; SGA, small-for-gestational age.

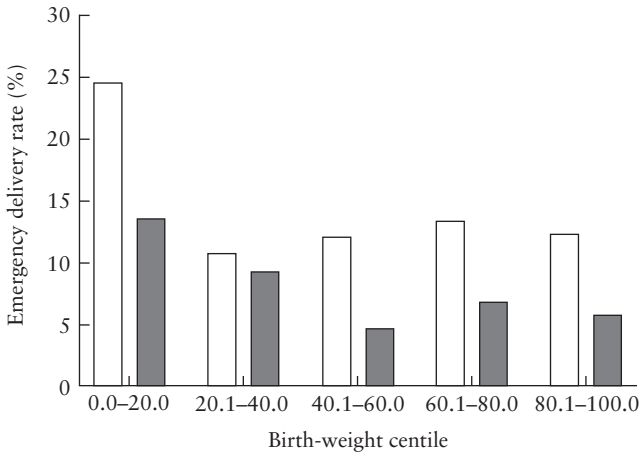

Figure 2 Rate of emergency delivery for presumed fetal compromise in women receiving epidural analgesia (□) and those receiving patient-controlled remifentanil analgesia (■), according to birth-weight quintile.

DISCUSSION

This *post-hoc* per-protocol analysis of the RAVEL study showed a significantly higher rate of emergency delivery for presumed fetal compromise in women receiving EDA compared with those receiving PCRA (14.8% *vs* 8.3%; OR, 1.69 (95% CI, 1.01–2.83)). Similar to the registry study of Damhuis *et al.*[6], we found an association between the background risk of emergency delivery for presumed fetal compromise, as defined by birth-weight quintile, and EDA, this association being modestly stronger at lower birth-weight quintiles. In this context, it is important to recognize that the incidence of emergency delivery for presumed fetal compromise (irrespective of type of pain relief) was highest in women delivering a neonate with a birth weight in the lowest quintile.

There has been much debate on the retrospective nature of the registry analysis and its possible biases and residual confounders. This *post-hoc* analysis of prospective data aimed to address those arguments; however, it calls for further, preferably randomized, analyses to strengthen the hypothesis of a causal relationship between use of EDA and emergency delivery for presumed fetal compromise. The main finding of the study of Damhuis *et al.*[6] was in line with that of the Cochrane review, which determined that more women in the EDA group needed instrumental vaginal birth than did those who received PCRA[2]. However, the Cochrane review found no difference in emergency Cesarean section rate for presumed fetal compromise between groups. This discrepancy can be explained by the Cochrane review methodology, as the analyses were performed as far as possible on an intention-to-treat basis. Crossover from PCRA to EDA is more likely due to the superior pain-relieving effect of EDA and, therefore, emergency Cesarean deliveries after crossover would have been recorded in the PCRA group, obscuring the association. The pooling of studies included in the Cochrane review would have carried forward the systematic masking of the hypothesized effect. To support our theory that crossover in the intention-to-treat analyses of the Cochrane review masked the associations with emergency delivery, we analyzed the crossover patterns in the RAVEL randomized controlled trial. Of the women who were randomized to PCRA but switched to EDA, 25.9% had an emergency delivery for presumed fetal compromise. This rate was higher than that in women who were randomized to EDA and subsequently received PCRA (15.1%).

The interaction between placental (dys)function and adverse outcome, including hypertensive disorders of pregnancy, fetal growth restriction and fetal compromise, is well-established[14–17]. Fetal smallness is a known proxy for this association, with a gradual relationship: the smaller the fetus, the higher the chance of placental dysfunction[7]. This study confirms this pattern, suggesting that fetuses already at increased risk of intrapartum hypoxia related to reduced placental function are more likely to develop this outcome when EDA induces (subclinical) maternal hypotension. Thus, intrapartum EDA use increases the background risk, determined by placental function, of the need for emergency delivery.

These findings should prompt more in-depth analysis and consideration regarding the administration of EDA for intrapartum pain management when infants are estimated to be at high risk of placental dysfunction. The implications for clinical practice are uncertain, as EDA is considered to be the most effective method of pain relief during labor[10]. Likely confounders for which no data were available in the RAVEL study, such as variation in clinical practice regarding EDA method and intrapartum management, could impact the association of EDA with emergency delivery for presumed fetal compromise. Because pain is influenced by emotion and motivation[18], it is possible that when women are informed of fetal compromise as a potential side effect of EDA, they may be inclined and able to use alternative or no pain relief. Innovative methods for pain relief, such as virtual reality, should be explored as a potential alternative to EDA in order to reduce the number of emergency deliveries for presumed fetal compromise, especially for mothers with small-for-gestational-age fetuses. Reduced use of EDA could mean that women experience more pain for undetermined benefit with regard to mode of delivery, as the background risk of emergency delivery for fetal compromise remains.

To further corroborate our findings, we would welcome a meta-analysis with individual patient data (IPDMA) of the studies that informed the Cochrane review[2]. Additionally, this study included pregnant women delivering between May 2011 and October 2012. It is worth noting that the Cochrane review[2] found that the higher rate of instrumental delivery following EDA was not observed in studies conducted after 2005. This might be attributed to the use of lower concentrations of local anesthetic and the adoption of more advanced epidural techniques, such as patient-controlled EDA, in more recent years. However, it is important to note that limited data are available regarding the shift in

EDA concentrations during this period in the RAVEL study patients. Therefore, future studies should seek to assess longitudinal trends in mode of delivery in order to understand fully the implications of these changes.

Strengths and limitations

A major strength of this study is that we used high-quality prospective data from a randomized controlled trial to support our hypothesis as to why our recent analysis of registry data contradicts the existing literature, including the Cochrane review.

A limitation of this study is that no information was available on maternal smoking, which is known to be a possible confounder. While this *post-hoc* per-protocol analysis benefits from the prospective nature of data collection in the RAVEL study, it cannot be considered a randomized comparison after excluding women who did not receive pain relief. Moreover, we did not have information regarding ultrasound findings of placental insufficiency, such as Doppler studies. Yet another potential limitation is residual confounding, despite correction for known confounders that were available, such as parity. Furthermore, the RAVEL study was not powered for this research question.

Conclusions

Intrapartum EDA is associated with a higher rate of emergency delivery for presumed fetal compromise compared to patient-controlled treatment with remifentanil. Birth-weight quintile is a strong predictor of emergency delivery for presumed fetal compromise, but does not mediate the effect of EDA. Pregnant women and their obstetric caregivers should be aware of these risks and could consider alternative pain relief. Future studies should seek to replicate these findings and explore alternatives to EDA with regard to pain relief, adverse effects and patient satisfaction.

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