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Duration of labor, delivery mode and maternal and neonatal morbidity after remifentanil patient-controlled analgesia compared with epidural analgesia

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ABSTRACT

Objective: The objective of this study was to compare duration of active labor, delivery mode, maternal and neonatal morbidity and women's satisfaction with delivery after intravenous remifentanil patient-controlled analgesia (PCA) or standard epidural analgesia (EDA). Based on clinical observations, we hypothesized that women with PCA would have shorter labor.
Study design: An observational study at a university hospital in Sweden 2009–16. Maternal and neonatal outcomes with PCA (n = 69) and EDA (n = 138) were compared.
Results: Women with PCA had shorter active labor 5.6 ± 3.3 compared to 8.5 ± 4.4 h ($p < 0.001$) with EDA, and a higher rate of spontaneous delivery 94% (65/69) compared to 65% (n = 90/138) with EDA ($p < 0.001$). Intrapartum temperature >38 °C ($p = 0.001$) and signs of fetal asphyxia ($p < 0.001$) were less common with PCA. No maternal or neonatal sedation was observed. The rates of transient oxygen desaturation <95%, bleeding > 1000 mL and women's satisfaction with delivery did not differ between the groups.
Conclusion: PCA had several advantages over EDA, as it was associated with shorter active labor and a higher rate of spontaneous delivery without worsening maternal or neonatal morbidity or women's satisfaction with delivery. Therefore, we suggest an increased availability of PCA for labor analgesia. We recommend continuous one-to-one care and oxygen saturation monitoring for all women during active labor.

Introduction

The ultra-short acting synthetic opioid remifentanil has recently been introduced for intravenous patient-controlled analgesia (PCA) during obstetric labor as an alternative to standard epidural analgesia (EDA). In Sweden, approximately 50% of primiparous women and 30% of multiparous women receive labor analgesia with EDA. Reports on negative effects associated with EDA such as prolonged labor, risk of instrumental delivery, spinal hematoma and urinary bladder retention have been conflicting [1,2]. The use of remifentanil PCA has been limited after reports on less analgesic effect compared with EDA, and fear of maternal sedation and neonatal asphyxia as intravenous opoids may cross the placental barrier [3–5]. The aim of this study was to compare labor outcome after labor analgesia with remifentanil PCA and standard EDA. Based on clinical observations, we hypothesized, that PCA would be followed by shorter labor. Furthermore, we compared delivery mode, maternal and neonatal morbidity, and women's satisfaction with delivery after the two methods for labor analgesia.

Material and methods

Ethics approval was obtained from the Regional Ethics Committee for Medical Sciences in Stockholm, Sweden, 9 April 2015, No 2014/255-31. Since all data were anonymized and were presented on a group basis only individual patient consent was not requested. Remifentanil PCA (Ultiva®, Aspen Nordic, Denmark) has been used for labor analgesia as an alternative to EDA at the Karolinska University Hospital since 2009. This retrospective cohort study was initiated as a student's Medical Degree Project at the Karolinska Institute and was performed without patient involvement. All data were collected by two physicians from electronic obstetric records (Obstetrix® Cerner AB, Stockholm, Sweden) by identification of the World Health Organization (WHO) International Classification of Diseases (ICD)-10 code

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SR.310 PCA for labor analgesia. All data were reviewed repeatedly to assure accuracy. Patient enrolment is shown in Fig. 1.

Remifentanil PCA group

The remifentanil PCA group included all singleton, term pregnant women (n = 69) who had labor induced between January 1 2009–December 31 2016 and received remifentanil PCA during the first stage of labor before cervical dilatation of 4–5 cm. In these women EDA was contraindicated due to coagulopathy, low molecular weight heparin (LMWH) prophylaxis or previous lumbar spinal injury. Labor was induced to allow for a specialist in anesthesiology to initiate PCA. Exclusion criteria were multiple pregnancies (n = 2) and spontaneous labor onset (n = 4). Based on previous studies, the patient-controlled device was programmed to deliver 0.1–0.8 μg remifentanil/kg (in a solution of 20 μg/mL) on request at the first sensation of pain, with a lockout time of two min to prevent the risk of respiratory depression [3]. The lowest dose of remifentanil (0.1 μg/kg) was initiated and increased as the intensity of pain increased to a maximum dose of 0.8 μg/kg. All women in the remifentanil PCA group received continuous one-to-one care during active labor and were instructed in the correct use of the PCA device by a midwife. Maternal respiration, sedation and nausea were monitored and documented in the obstetric record. If requested by these women, a mixture of oxygen and nitrous oxide (50:50%) was added for analgesia.

Standard EDA group

The matched EDA control group included singleton, term pregnant women (n = 138) who had labor induced between January 1st 2009–December 31st 2016 and received standard EDA with bupivacaine (Bupivacaine® Accord Health Care AB) and sufentanil (Sufenta® Piramal Critical Care BV) during the first stage of labor before cervical dilatation of 4–5 cm. Two investigators identified the women in the control group, who were matched to the women in the study group regarding the factors known to influence labor progress - age, parity, gestational age, cervical score, induction method, prior CS and body mass index (BMI). Similar to the study group, a mixture of oxygen and nitrous oxide (50:50%) was added for analgesia if requested by these women. All women in the EDA group received continuous one-to-one care during active labor. All records were verified to assure accuracy.

The induction method was chosen by an obstetrician after digital assessment of the cervical score. It was categorized according to the standard modified Bishop Score (BS) model monitoring cervical dilatation, effacement, consistency and position [8]. In case of a ripe cervix with a BS > 5 points labor was induced by artificial rupture of the fetal membranes (amniotomy). In case of an unripe cervix with a BS < 5 points, labor was induced with transcervical catheter, oral prostaglandin (PG)-E_1 or vaginal PG-E_2 gel. Labor induction with a catheter was carried out with insertion of a 22 Charrière Foley catheter (Meteko Instruments, Sweden) into the intrauterine, extraamniotic space at speculum investigation or digital examination. The catheter balloon was filled with sterile water 50 mL and the position was controlled by traction every 30 min. Amniotomy was made immediately after catheter expulsion. An infusion of Oxytocin 5 U in 500 mL saline was started one hour after amniotomy if no uterine contractions were observed, and immediately after catheter expulsion in women with pre-labor rupture of the fetal membranes. Labor induction with oral PG-E_1 was carried out with the smallest available PG-E_1 tablet (esterified PG-E_1 analogue misoprostol Cytotec®, Pfizer, Sweden) 200 μg dissolved in 20 mL of water resulting in a concentration of 10 μg/mL [9]. A solution of 2.5 mL containing 25 μg of misoprostol was aspirated in a syringe, whereupon the woman sprayed the solution followed by water in her mouth. Treatment with a new dose of 25 μg in solution was continued every second hour until labor onset up to a maximum of 8 doses. Labor induction with vaginal PG-E_2 gel (endogenous PG-E_2 dinoprostone, Minprostin®, Pfizer, Sweden) was application of PG-E_2 gel 2 mg in the posterior vaginal fornix every 6–8 h up to a maximum of 3 doses. Women's satisfaction with delivery was scored according to clinical routine with a standard visual analogue scale (VAS) 0–100 mm, where 0 = worst imaginable and 100 = best imaginable experience, before discharge from the obstetric unit.

The definition of active labor was the interval between cervical dilatation of 4–5 cm and childbirth during all years studied. It was assessed by clinical examination of a midwife or an obstetrician and was recorded in the electronic obstetric partogram. The definition of prolonged labor (labor arrest) was failure to progress for more than 3–4 h during the first stage or more than 2–3 h during the second stage. Maternal oxygen saturation and pulse was continuously monitored using a pulse oximeter, and intermittent manual non-invasive blood pressure measurement was recorded during all deliveries. The fetal heart rate was monitored with

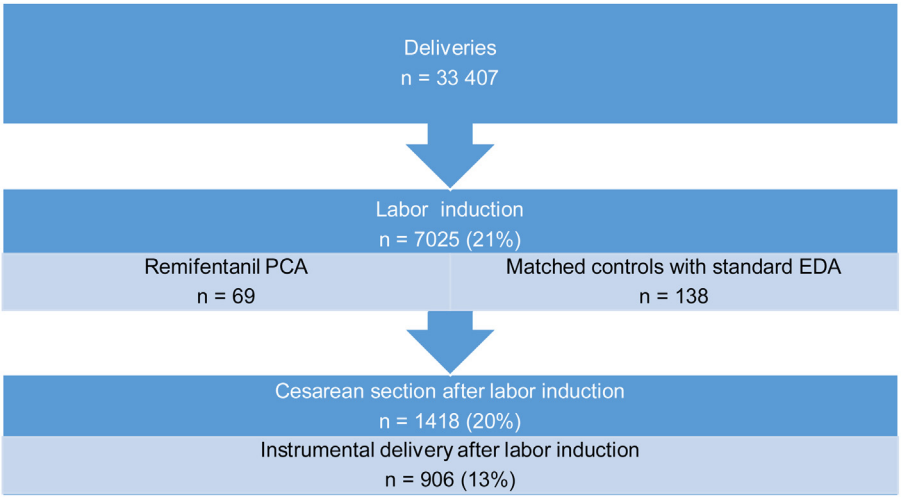

Fig. 1. Participant flow diagram. Obstetric data January 1 2009 – December 31 2016.
Abbreviations: Epidural analgesia (EDA), patient-controlled analgesia (PCA).

continuous cardiotocography (CTG) during active labor. Signs of fetal asphyxia were a pathological CTG registration or a pathological scalp-lactate blood sample >4.8 mmol/L. Signs of neonatal asphyxia were Apgar score <7 points at 5 min, umbilical artery base excess (BE) exceeding −10 mmol/L or other signs or symptoms of neonatal distress necessitating Neonatal Intensive Care Unit (NICU) admission.

Outcomes

The primary outcome was the duration of active labor. Secondary outcomes were delivery mode, maternal and neonatal morbidity and women's satisfaction with delivery. The analgesic effect of remifentanil PCA compared to EDA has been evaluated by others, and such data were not collected here.

Statistical methods

Based on clinical observations, we assumed that remifentanil PCA would be associated with a 50% decrease of active labor duration from 10–5 h. According to a power analysis, a sample size of n = 32 in each group would be needed when aiming a significance level of 5% and a power of 80%. A two-tailed p-value <0.05 was considered significant. Continuous data were analyzed using Mann Whitney *U* test and General Linear Model when appropriate and categorical data with One way ANOVA. Continuous data were presented as means ± SD and categorical data as numbers and percentages.

Results

Maternal data are shown in Table 1. The PCA group and matched EDA group were comparable regarding the factors known to influence labor progress – maternal age, gestational age, parity, cervical score, induction method, prior CS and BMI. All women in the PCA group received PCA only, and all women in the EDA group received EDA only. No other opioids were administered in either group. Indications for labor induction are shown in Table 2 and induction methods in Table 3. In both groups the mean gestational age at delivery was 39–40 weeks, and the induction methods were transcervical catheter in 43%, amniotomy in 30%, vaginal PG-E_2 gel in 13%, and oral PG-E_1 in 13%. In the PCA group, the indication coagulopathy included idiopathic thrombocytopenic purpura (n = 32/46), von Willebrand's disease (n = 11/46), dysfibrinogenemia (n = 2/46) and haemophilia (n = 1/46). In the EDA group, the major indications were post-term pregnancy (n = 25/138), hypertensive disease (n = 23/138) and pre-labor rupture of the fetal membranes (n = 20/138). Other indications (n = 70/138) included gestational diabetes, anemia, pregnancy ailments and fear of vaginal delivery.

Maternal outcomes are shown in Table 4. Women with PCA had shorter active labor 5.6 ± 3.3 h compared to 8.5 ± 4.4 h with EDA (p < 0.001), and shorter induction to delivery interval 13.4 ± 9.4 h compared to 16.1 ± 8.4 h with EDA (p = 0.003). The rates of CS 3% (n = 2/69) and instrumental delivery 3% (n = 2/69) with PCA were lower than the rates of CS 17% (n = 24/138) and instrumental delivery 17% (n = 24/138) with EDA (p < 0.001). In the PCA group, only occasional operative 0.1% (n = 1/69) and instrumental 0.1% (n = 1/69) deliveries were performed because of prolonged labor in contrast to the EDA group, where several operative 14% (n = 19/138) and instrumental 12% (n = 17/138) deliveries were carried out on this indication. Likewise, only occasional operative 0.1% (n = 1/69) and instrumental 0.1% (n = 1/69) deliveries were performed because of fetal asphyxia in the PCA group in contrast to the EDA group, where several operative 4% (n = 5/138) and instrumental 5% (n = 7/138) deliveries were carried out for this indication (p < 0.05). The rates of maternal temperature >38.0 °C was lower 3% (n = 2/69) with PCA compared to 19% (n = 27/138) with EDA (p = 0.001), as were signs of fetal asphyxia 3% (n = 2/69) with PCA compared to 22% (n = 31/138) with EDA (p < 0.001). Nausea was more common after PCA 16% (n = 11/69) compared to 9% (n = 12/138) with EDA (p = 0.04). No cases of maternal sedation were observed. The rate of transient oxygen desaturation <95% was low 3% (n = 2/69) with PCA and none with EDA (p = 0.87), as was the rate of postpartum bleeding >1000 mL 11% (n = 8/69) with PCA and 10% (n = 14/138) with EDA (p = 0.72). Low dose LMWH (dalteparin, Fragmin®, Pfizer, Sweden) prophylaxis 5000 U daily was more common 22% (n = 15/69) in the PCA group compared to 3% (n = 4/138) in the EDA group (p < 0.001). A subgroup analysis of the PCA group showed that active labor was 6.9 ± 4.4 h in women with LMWH compared to 5.2 ± 2.8 h in women without LMWH (p

Table 1
Maternal data. Statistical methods Mann Whitney *U* test and General Linear Model when appropriate[1] and One Way ANOVA[2].

Variable	PCA n = 69	EDA n = 138	p value
Age, years (mean ± SD)	32 ± 5.7	32 ± 5.3	0.50[2]
BMI, kg/m^2 (mean ± SD)	24.9 ± 7.2	25.8 ± 5.0	0.25[2]
Primiparous, n (%)	33 (48)	68 (49)	0.92[2]
Prior cesarean, n (%)	6 (9)	14 (10)	0.76[2]
Cervical score (mean ± SD)	4.6 ± 1.9	4.2 ± 1.9	0.10[1]

Abbreviations: EDA=epidural analgesia, PCA=patient-controlled analgesia, PG=prostaglandin.

Table 2
Indications for labor induction.

PCA n = 69 (%)		EDA n = 138 (%)	
Coagulopathy	46 (67)	Postterm pregnancy	25 (18)
LMWH prophylaxis	14 (20)	Hypertensive disease	23 (17)
Lumbar spinal injury	9 (13)	Prelabor rupture of fetal membranes	20 (14)
		Other	70 (51)

Abbreviations: EDA=epidural analgesia, LMWH=low molecular weight heparin, PCA=patient-controlled analgesia.

Table 3
Induction methods.

Variable	PCA n = 69 (%)	EDA n = 138 (%)
Catheter	30 (43)	60 (43)
Amniotomy	21 (30)	42 (30)
Vaginal PG-E_2	9 (13)	18 (13)
Oral PG-E_1	9 (13)	18 (13)

Abbreviations: EDA = epidural analgesia, LMWH = low molecular weight heparin, PCA = patient-controlled analgesia, PG = prostaglandin.

Table 4
Maternal outcomes. Statistical methods Mann Whitney *U* test and General Linear Model when appropriate[1] and One Way ANOVA[2].

Variable	PCA n = 69	EDA n = 138	p value
Delivery mode, n (%)			<0.001[2]
Spontaneous	65 (94)	90 (65)	
Instrumental	2 (3)	24 (17)	
Cesarean	2 (3)	24 (17)	
Active labor, hours (mean ± SD)	5.6 ± 3.3	8.5 ± 4.4	<0.001[1]
Sedation, n (%)	0	0	
Saturation <95%, n (%)	2 (3)	0	0.32[2]
Temperature >38 °C, n (%)	2 (3)	27 (19)	0.001[2]
Nausea, n (%)	11 (16)	12 (9)	0.04[2]
Signs of fetal asphyxia, n (%)	2 (3)	31 (22)	<0.001[2]
Bleeding >1000 mL, n (%)	8 (11)	14 (10)	0.72[2]
Satisfaction delivery, n (%)	59 (85)	98 (71)	
VAS scale, mm (mean ± SD)	71 ± 23	71 ± 23	0.99[1]

Abbreviations: EDA = epidural analgesia, PCA = patient-controlled analgesia, VAS = visual analogue scale.

Table 5
Neonatal outcomes. Statistical methods Mann Whitney U test and General Linear Model when appropriate[1] and One Way ANOVA[2].

Variable	PCA n = 69	EDA n = 138	p value
Birth weight >4500 g, n (%)	0	5 (4)	0.11[2]
Apgar <7 at 5 min, n (%)	1 (1)	2 (1)	0.99[2]
BE(a) −10 mmol/L, n (%)	64 (93)	127 (92)	
	6 (9)	12 (9)	0.99[2]
NICU admission, n (%)	1 (1)	6 (4)	0.29[2]
Sedation, n (%)	0	0	

Abbreviations: BE(a)=base excess umbilical artery, EDA = epidural analgesia, NICU = Neonatal Intensive Care Unit, PCA = patient-controlled analgesia.

= 0.26). One of two women women in the PCA group who went through an operative delivery (n = 2/69) had LMWH prophylaxis. Likewise, one of two women in the PCA group who went through an instrumental delivery (n = 2/69) had LMWH prophylaxis. Women's satisfaction with delivery according to VAS scoring was comparable 71 ± 23 mm (n = 59/69, 85% documented answer rate) after PCA and 71 ± 23 mm (n = 98/138, 71% documented answer rate) after EDA (p = 0.99).

Neonatal data are shown in Table 5. The rate of birth weight >4500 g none (n = 0/69) in the PCA group and 4% (5/138) in the EDA group did not differ (p = 0.11). The mean birth weight was comparable between the groups regardless of delivery mode (data not shown). The rate of Apgar score <7 at 5 min was 1% in both PCA (n = 1/69) and EDA (n = 2/138) groups (p = 0.99), and the incidence of BE(a) exceeding −10 mmol/L was 9% in both PCA (n = 6/69) and EDA (n = 12/138) groups (p = 0.99). There were no cases of neonatal sedation, intrauterine fetal death or neonatal death.

Discussion

We have compared the duration of active labor, delivery mode, maternal and neonatal morbidity and women's satisfaction with delivery after labor analgesia with remifentanil PCA and standard EDA initiated before cervical dilatation of 4–5 cm.

Our results showed, that women with PCA had shorter active labors compared to women with EDA. Moreover, the rates of operative and instrumental delivery were lower with PCA. These results were observed without worsening of maternal or neonatal morbidity or women's satisfaction with delivery. Intrapartum maternal fever and intrapartum signs of fetal asphyxia were less common with PCA, although nausea was more common. Cases of transient maternal oxygen desaturation were few and comparable with the two analgesic methods. No cases of maternal or neonatal sedation were observed. The rate of postpartum bleeding >1000 mL and signs of neonatal asphyxia did not differ.

The rates of operative and instrumental delivery in women with PCA were low also when compared to the general rates of operative 20% and instrumental 13% delivery after induced labor at our obstetric unit during the years studied. Our finding that women with PCA had shorter active labor is of clinical importance, since most operative and instrumental deliveries are performed because of prolonged labor [6,7]. This was evident in the present study, where the majority of the cesareans and instrumental deliveries in the EDA group were carried out on this indication. Factors that promote spontaneous delivery also promote maternal health, since cesareans increase the risk of perioperative bleeding and postoperative infection as well as pathologic placentation, peripartum hysterectomy and massive obstetric bleeding in a subsequent pregnancy, whereas instrumental delivery increases the risk of perineal lacerations [10,11].

The reasons behind the shorter active labor and higher rate of spontaneous delivery in the PCA group could be that women with PCA were able to control their analgesic administration themselves and readily when needed. This would reduce stress and promote labor progress, since acute stress hormones suppress uterine activity and counteract labor progress. Consequently, the anti-stress hormone oxytocin stimulates labor progress [12–15]. One-to-one care during delivery has been reported to promote labor progress, possibly by increasing the release of endogenous oxytocin [14,16]. This would not have been a confounder in this study, since continuous one-to-one care was provided in both groups during active labor.

Several authors report increased risks of prolonged labor and instrumental delivery in women with EDA compared to women without EDA [1,2]. Women with EDA have lower plasma concentration of endogenous oxytocin, and require labor augmentation with intravenous oxytocin more often than women without EDA [1,17]. The reason, according to experimental studies, is that EDA blocks a spinal reflex release of oxytocin and subsequently prostaglandin F, which results in prolonged labor. Furthermore, lumbar spinal blockage by transection of the vagal or pelvic nerves suppress cervical ripening and uterine contractions and delays birth [18,19].

We found, that women's satisfaction with delivery was comparable after PCA and EDA. This was in accordance with previous studies, where women's satisfaction with pain relief was comparable with the two methods when asked in retrospect [3,4,20–22]. Although EDA is reported to provide a more effective pain relief when measured during active labor, women appear to consider other favourable factors to be important at delivery than the effectiveness of pain relief [22].

Our results were in agreement with a previous study on remifentanil PCA for labor analgesia, where the authors report that it provides adequate pain relief and high maternal satisfaction during the first and second stages of labor, and was associated with a low CS rate 7% (n = 3/41). The authors conclude that transient maternal oxygen desaturation may occur, but no serious neonatal side effects were observed [20]. Our results differed partly from another study comparing remifentanil PCA (n = 402) with EDA (n = 296), which reports less intrapartum fever, but a higher rate of transient oxygen desaturation <95% and nausea with PCA, and comparable delivery modes with the two methods [21]. However, the results may be biased since 24% of women with PCA also received EDA and some women were treated with other opoids, whereas 17% of women with EDA also received other intravenous opioids. A recent study comparing remifentanil PCA (n = 94) with EDA (n = 76) reports a higher rate of transient maternal desaturation <95% after PCA, and comparable delivery modes with the two methods [22].

Strengths and limitations

Strengths of this study included data collected from original electronic obstetric records, that women in the PCA group received PCA only and women in the EDA group received EDA only, and that the sample size was accurate according to a power analysis. The observational design was a limitation. It may be questioned, whether the different indications for labor induction was a confounder. However, controls were matched to the study participants regarding factors that influence labor progress – maternal age, gestational age, parity, cervical score, induction method, prior CS and BMI. Therefore, we don't consider the different indications to be a confounder. Low dose LMWH prophylaxis was more common in the PCA group than in the EDA group. This might have been a confounder, since treatment with LMWH 5000–15 000 U daily has been suggested to promote or counteract labor progress [23,24]. However, a subgroup analysis of our results showed that neither duration of active labor nor

delivery mode differed between women with LMWH compared to women without LMWH.

In conclusion, labor analgesia with remifentanil PCA had several advantages over standard EDA, as it was followed by shorter active labor and a higher rate of spontaneous delivery without worsening maternal or neonatal morbidity or women's satisfaction with delivery. Therefore, we suggest an increased availability of PCA for labor analgesia. We recommend continuous one-to-one care and oxygen saturation monitoring for all women during active labor.

Declaration of Competing Interest

As the corresponding author I declare on behalf of all authors - Anna Thorbiörnson, Paula da Silva Charvalho, Anil Gupta and Ylva Vladic Stjernholm - that there have been no involvements that might raise the question of bias in the work reported, or in the questions, implications or opinions stated.

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