Remifentanil by Patient Controlled Analgesia Compared with Epidural Analgesia for Pain Relief in Labour

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ABSTRACT

Back ground: *Epidural analgesia has been established as the gold standard for labour analgesia. However, clinical contraindications and personnel or institutional limitations preclude some parturients from receiving an epidural. Remifentanil has been suggested as an ideal opioid for patient controlled analgesia (PCA) in labour. In our study we compared the use of PCA remifentanil to epidural analgesia in labour as regard pain relief, safety of the mother and the fetus, side effects, and overall parturient's satisfaction.*

Methods: *After ethical committee approval and informed written consent 30 healthy pregnant women ASA I or II, with no obstetric complications or contraindication to remifentanil or epidural analgesia were included in the study randomly allocated into one of two equal groups, in (Group EP) epidural infusion of bupivacain 1% plus 2ug/ml of fentanyl was given and in (Group R) the women received PCA remifentanil with a bolus of 0.4 ug kg^{-1} over 20 seconds and a lockout period of 1 min as an analgesia for labour.*

Results: *There was significant decrease in (VAS) of pain in both groups with significantly more decrease in (Group EP). There were no significant difference between both groups as regard arterial blood pressure, heart rate, oxygen saturation, nausea, and overall patient's satisfaction. Sedation scores were significantly higher in (Group R), there were no serious bradycardia, hypotension, or desaturation, and all the parturients were easily arousable.*

There were no fetal heart rate changes that required interference. The median 1 & 5 minutes Apgar scores were 9 in both groups, and the mean umbilical cord gases, & lactate levels were within normal limits with no difference between both groups.

Conclusion: *Our study demonstrated that epidural infusion gives superior analgesia for labour than PCA remifentanil, however PCA remifentanil is a good, safe, and could be an alternative method of analgesia for labour.*

Key words: *Remifentanil, PCA, Epidural analgesia, labour .*

INTRODUCTION

Lumbar epidural analgesia has established itself as the gold standard for labour analgesia. However, clinical contraindications (coagulopathy, anatomical abnormality and infection) and personnel or institutional limitations preclude some parturients from receiving an epidural. Also, 10—15% of all epidural anesthetics result in incomplete pain relief(1). Alternatives to epidurals such as opioids and nitrous oxide provide inferior analgesia and are associated with a higher incidence of neonatal depression and adverse maternal psychological effects(2).

Remifentanil hydrochloride is the latest short-acting synthetic opioid introduced to practice in 1993. Remifentanil is a selective µ-opioid receptor agonist having a methyl-ester linkage that makes it susceptible to metabolism by esterases in blood and other tissues to almost completely inactive metabolites, which are eliminated in the urine, with a very short context-sensitive half-life (3-6 min.)(3). The pharmacokinetic and pharmacodynamic profile of remifentanil suggests that this agent is highly titratable with a predictable offset of action. Indeed, the rapid metabolism of remifentanil results in a rapid transition from intense analgesia to minimal residual effect[4].

Remifentanil has been administered as a patient controlled analgesia (PCA) to provide pain relief in labour with minimal side-effects for both mother and fetus[5]. Comparative studies have shown that Remifentanil PCA provides better analgesia during labour than intermittently inhaled nitrous oxide, and a greater analgesic efficacy than intramuscular and intravenous meperidine[6,7].

In this study we aimed to compare the use of PCA remifentanil to epidural analgesia in labour as regard pain relief, safety to the mother and the fetus, side effects, and overall parturient's satisfaction.

PATIENTS AND METHODS

After approval from the hospital ethics committee, written informed consent was obtained in the preanesthesia clinic at the 36th week of gestation for enrollment in the study. 30 healthy women with singleton pregnancies ASA I or II, with no known obstetric complications were included in the study randomly allocated into one of two equal groups using sealed envelop technique receiving either, epidural analgesia for labour pains (Group EP), or patient controlled analgesia using remifentanil (Group R). The exclusion criteria were any contraindication to remifentanil or epidural analgesia, and the women who refused either of the techniques were excluded from the study. The study was started when All women were in active labor (cervical dilation of 3–6 cm).

In group R the women received PCA with a remifentanil bolus of 0.4 ug kg^{-1} over 20 seconds and a lockout period of 1 min, with no maximum hourly limit or backword infusion. A 16 gauge cannula was inserted with local anaesthesia attached to a line providing continuous infusion of saline at approximately 100ml h^{-1} and the PCA was connected using (Baxter PCA II, (Baxterhealthcare corporation),Deerfield, IL60015 USA, Singapor made.) The parturients were instructed to use the PCA at the first sign of a forthcoming uterine contraction not at the maximal pain of the contraction. One of the investigators (an anaesthetist) remained on the delivery suite for the duration of use of PCA to provide continuous monitoring and attended to the mother throughout the entire labour. Suplemental oxygen by nasal cannula 2 l min^{-1} was started if oxygen saturation reaches 92% in all the parturients. The women used the PCA from institution until after delivery of the placenta. If they decided to withdraw from the study because of inadequate pain relief, the remifentanil PCA was to be used until an epidural had been sited.

In group EP an epidural catheter was inserted under strict aseptic technique in L3-4 intervertebral space and a bolus of (15ml) bupivacain 1%plus 2ug/ml of fentanyl was given then an infusion of (6-10) ml hr^{-1} of the same solution was started epiduraly with top up doses of the same concentration (10ml) if the pain score is above 40mm when the woman is fully dilated a bolus of (15ml) is given for the second stage with the parturient in the head up position.

A visual analogue scale (VAS) scoring system was used to assess the average level of pain, VAS scores were recorded immediately before the PCA or epidural analgesia was started (baseline VAS scores) and hourly throughout the first and second stages of labour. This consisted of a 100 mm horizontal line with a verbal description at either end ('no pain' and 'worst pain imaginable'). VAS score for the subject's level of pain overall throughout labour was also recorded within 30 min of delivery (postdelivery score). Pulse oximetry and heart rate were monitored continuously, non-invasive blood pressure and ventilatory frequency were recorded hourly. The hourly sedation score was noted using a four-point scale (1=alert; 2=slightly drowsy but alert to voice; 3=drowsy but responds to gentle stimulus; 4=very drowsy). The patients scored the presence and the intensity of nausea, and itching (four point rank score: none, slight, moderate, or severe).

The fetal heart rate (FHR) was monitored with a cardiotocograph (Corometics 120 Series, GE Medical Systems) for the first 20 min after starting the PCA and for a subsequent 20 min period every 2 h throughout labour, or more often if indicated. The FHR tracings were analyzed by an obstetrician and categorized as normal, suspicious or pathological, according to current NICE guidelines(8). The category was determined by assessing baseline, variability, decelerations and accelerations in each FHR trace. Umbilical artery (UA) blood samples were obtained for pH values and lactate measurement at the time of delivery. Apgar scores at 1 and 5 min were noted. Patient characteristics and obstetric data were collected and these results were summarized.

SPSS 10.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Student's t test was used for the comparison of parametric data and the chi square test was used for the comparison of the non parametric data. P values < 0.05 were considered statistically significant.

RESULTS

Thirty women were enrolled in this study, fifteen in each group with no statistically significant difference between them as regard demographic and obstetric data (Table I). Two women in each group had undergone cesarean section for delivery, they were included in the study as regard the visual analogue scale for pain, hemodynamic data and sedation scores, but the neonatal cord blood gases were not included in the R group as it could be affected by the general anesthesia both women received.

There was statistically significant decrease in VAS for pain from the baseline in both groups, but it was significantly decreased more in the EP group (Figure 1). However there was no statistically significant difference between both groups regarding the postdelivery VAS for overall pain during the delivery (Table IV).

On the four point sedation scale women in the R group were significantly more sedated than those in the EP group, but sedation score was never more than 2 (slightly drowsy but alert to voice) (Table II). There was no evidence of maternal muscle rigidity or respiratory rate <12 bpm, and the lowest oxygen saturation recorded was 92%. Only two women needed supplemental oxygen in the R group. There were no statistically significant difference between both groups as regard MABP, HR, RR, and SPO_2 (Table III). Only two patients in the R group had mild itching and didn't require any treatment, while two patients had slight nausea in both groups.

Table I: Patient characteristics and obstetric data. Data are mean (range) or mean (SD)

	Group EP (n=15)	Group R (n=15)
Age (yr)	30 (23-40)	27 (18-38)
Weight (kg)	70.5 (16.1)	68.6 (15.8)
Primiparous/Multiparous	6/9	5/10
Duration of labour (min)	551 (101)	569 (106)
Spontaneous delivery (n)	10	11
Instrumental delivery (n)	3	2
Cesarean section (n)	2	2

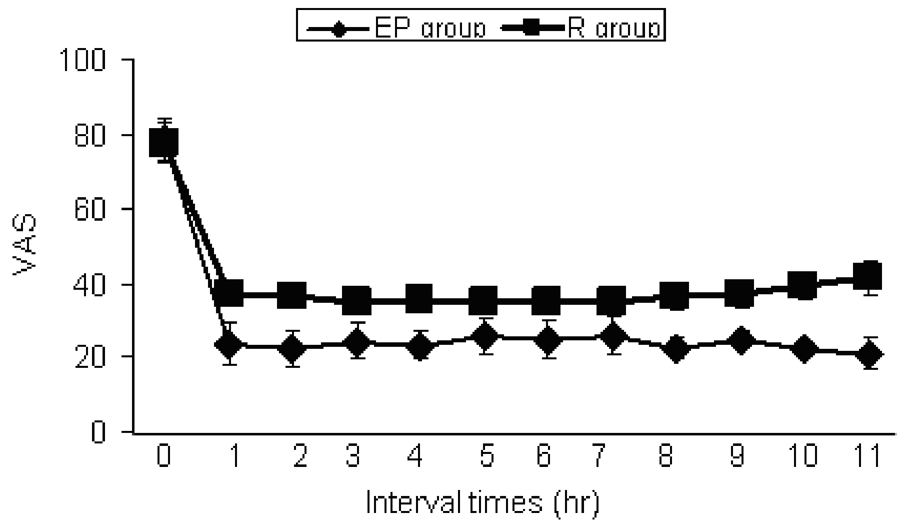

Fig.1 Comparison between the two studied groups regarding VAS.

Table II: Comparison between the two studied groups regarding Sedation score at different periods.

Time (hr)	Score	Group EP		Group R		p
		No.	%	No.	%	
Baseline	1	15	100.0	15	100.0	-
	2	0	0.0	0	0.0	
1	1	14	93.3	8	53.3	0.0021*
	2	1	6.7	7	46.7	
2	1	15	100.0	6	40.0	0.001*
	2	0	0.0	9	60.0	
3	1	14	93.3	5	33.3	0.0003*
	2	1	6.7	10	66.7	
4	1	15	100.0	4	26.7	0.001*
	2	0	0.0	11	73.3	
5	1	12	80.0	2	13.3	0.0001*
	2	3	20.0	13	86.7	
6	1	14	93.3	6	40.0	0.039*
	2	1	6.7	9	60.0	
7	1	12	100.0	5	38.5	0.001*
	2	0	0.0	8	61.5	
8	1	9	60.0	3	25.0	0.001*
	2	0	0.0	9	75.0	
9	1	7	100.0	0	0.0	0.0001*
	2	0	0.0	7	100.0	
10	1	4	100.0	2	50.0	0.023*
	2	0	0.0	2	50.0	
11	1	2	100.0	1	33.3	0.042*
	2	0	0.0	2	66.7	

Table III: Comparison between the two studied groups regarding vital signs and oxygen saturation

		Interval times (hr)											
		Base line	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Mean arterial blood pressure (mmHg)													
EP group	Mean	84.47	84.53	82.60	83.13	84.93	84.40	84.47	83.50	85.00	87.29	87.25	87.50
	S.D.	9.20	7.16	7.12	6.16	7.62	7.73	6.45	7.57	6.91	5.85	5.25	3.54
R group	Mean	84.13	83.60	83.00	82.60	83.93	83.60	83.40	83.31	84.00	85.00	84.50	84.33
	S.D.	7.54	6.34	6.27	4.48	6.58	6.42	6.42	7.59	5.85	7.59	7.72	6.03
Heart rate (Beat per minute)													
EP group	Mean	77.67	77.87	77.80	77.73	77.27	77.80	76.67	77.58	74.00	72.14	72.50	77.50
	S.D.	6.52	7.37	7.91	8.13	7.12	7.81	8.04	7.38	7.55	6.69	7.59	7.78
R group	Mean	77.73	77.73	77.93	78.40	77.60	77.00	77.40	77.62	75.83	73.00	69.75	69.33
	S.D.	7.26	8.15	7.11	9.33	7.53	6.93	8.11	8.37	6.73	6.45	2.63	3.79
Respiratory rate (Breath per min)													
EP group	Mean	17.80	16.80	16.67	17.20	17.67	17.27	17.73	18.17	18.56	17.29	17.25	17.50
	S.D.	1.78	1.93	2.06	1.70	1.72	1.67	1.53	1.80	2.19	0.95	1.26	2.12
R group	Mean	18.00	16.80	16.80	17.27	17.53	17.47	17.87	17.46	17.83	17.57	16.50	18.33
	S.D.	1.60	1.97	1.74	1.62	1.92	1.77	1.46	1.71	2.29	1.99	2.08	0.58
Oxygen saturation SPO_2 (%)													
EP group	Mean	97.20	97.60	97.20	97.27	97.53	97.33	97.47	96.83	97.22	97.57	97.50	97.50
	S.D.	0.77	0.83	1.01	0.80	0.74	0.90	0.99	0.83	0.44	0.53	0.58	0.71
R group	Mean	97.27	97.47	97.80	97.67	97.47	96.67	97.33	97.08	97.25	97.29	97.25	97.67
	S.D.	0.96	0.64	0.68	1.05	1.06	1.40	1.05	0.95	0.97	0.95	0.96	1.53

Table IV: Comparison between the two studied groups regarding Post delivery VAS overall pain throughout labour and neonatal data. Apgar scores are presented as median (range) Post delivery VAS overall pain throughout labour and umbilical cord blood gases as mean (SD)

Variables	Group EP	Group R	P
Post delivery VAS overall pain throughout labour	42.1 (6.7)	40.4(12.4)	0.72
APGAR score at 1 min.	9 (5-10)	9 (6-10)	0.33
APGAR score at 5 min.	9 (7-10)	9 (7-10)	0.37
Umbilical artery Ph	7.25 (0.05)	7.24 (0.04)	0.405
Umbilical vein pH	7.31 (0.04)	7.32(0.04)	0.41
Umbilical artery base excess (mEq $litre^{-1}$)	-5.19 (1.88)	-4.93(2.20)	0.38
Umbilical vein base excess (mEq $litre^{-1}$)	-2.34 (1.77)	-2.59 (0.94)	0.32
Umbilical artery lactate (mmol $litre^{-1}$)	4.14 (0.97)	4.33 (0.74)	0.268
Umbilical vein lactate (mmol $litre^{-1}$)	3.89 (0.93)	4.07 (0.77)	0.28

FHR traces were categorized as normal before starting PCA remifentanil or epidural analgesia in all women. There were two cases with early decelerations and one case had reduced beat to-beat variability in the R group, while In the EP group two cases had reduced beat to-beat variability .Apgar scores were (8, 8, 7, 8,and 9) at1 minute and (9, 8, 9, 9 and 9) respectively for the five neonates, Cord blood results were all in the normal rang. In R group one case had a low FHR and delivered with emergency cesarean section and was found to have the umbilical cord twisted around the baby's neck twice. Apgar scores for that baby were 5 & 8 at 1 & 5 minutes respectively, afterwards, the baby has improved markedly and systemic and neurological examination as well as routine lab work showed that he was completely normal.

The median 1 and 5 minute Apgar score was 9 in both groups. The mean cord blood gases and lactate levels were with in normal limits with no significant difference between both groups (Table IV).

DISCUSSION

Epidural infusion of local anesthetic with narcotic is the gold standard for analgesia in labour, and the routine method used in our institution, but it has some limitations. Remifentanil given by PCA has been noted to provide effective pain relief during labour and has shown superiority over nitrous oxide and intramuscular mepridine[6,7]. In order to evaluate the PCA remifentanil as a safe and efficient method of analgesia in labour, it was important to compare it to epidural analgesia in labour.

The bolus dose of remifentanyl used 0.4 ug kg^{-1} over 20 seconds and a lockout period of 1 min was used as it was the median effective dose used in previous study[9].

The main finding in this study was that both methods offers significant reduction in pain scores, which was significantly more in the epidural group as expected. This difference can be explained as the bolus dose of remifentanil was fixed, ideally the dose should be tailored to the individual patient and adjustments made as necessary with the progression of labour, especially as acute tolerance can develop with prolonged use of remifentanil[10]. Also in spite of teaching the parturients the optimal timing to press the PCA, sometimes there was delay in pressing with consequent peak effect of remifentanil after the uterine contraction. In spite of the significant difference as regard pain scores between both groups the overall pain score or patient's satisfaction was similar between groups, as using a PCA device can improve satisfaction scores in the clinical setting and itself affect the severity of pain. With the PCA system, the patient benefits from a greater sense of control over her pain management, an important psychological effect which contributes to the success of this technique[11]. All women who had received remifentanil PCA commented on the controllability of the PCA, which was considered as an advantage. Also the institution of PCA could be more satisfactory and less stressful than the application of epidural catheter.

Parturients in the Remifentanil group were significantly more sedated; however, all of them remained conscious and responsive. There was no evidence of haemodynamic instability or respiratory depression, in both groups. This is in agreement with the study of Volmanen et al who compared PCA remifentanil to nitrous oxide in labour analgesia, and found that sedation with remifentanil was minimal and didn't require any intervention. They also didn't have any case of desaturation as they were giving supplemental oxygen to all the women[7]. Volikas et al studying the maternal and neonatal side-effects of remifentanil PCA in labour had similar results with no haemodynamic instability nor desaturation below 93%, and the sedation effect of remifentanil was mild and all the women were alert to voice[5]. In other studies oxygen desaturation requiring oxygen supplementation has been demonstrated in the parturient receiving remifentanil PCA, but at a dose of 0.5 mg kg^{-1} and 2 min lockout the desaturation period was self limiting[9,12]. Volmanen et al in an earlier study of remifentanil in obstetric analgesia stated that during the administration of remifentanil, most of the patients had periods of oxygen desaturation. The incidence of desaturation increased toward the end of the study and decreased after the discontinuation of the drug[9]. With respect to oxygen saturation, however, short periods of remifentanil analgesia may be no worse than other forms of analgesia. Hemoglobin oxygen desaturation has also been reported during nonmedicated labor, labor with epidural analgesia or IV opioids, and combined analgesia with IM meperidine and nitrous oxide[13,14].

Two parturients had itching in the R group, this was generally mild and no treatment was required. Itching has previously been reported as a side-effect of remifentanil PCA during labour[12,15].

Nausea and vomiting are common during labour, but in our study remifentanil PCA resulted in no statistically significant change in the level of nausea than epidural analgesia. This is consistent with a previous study administering the same dose of remifentanil[12].

There were no significant differences between both groups as regard analysis of cardiotocographs. Most of the suspicious and pathological traces were recorded during the second stage of labour, when analysis can be difficult. There was no association between commencement of PCA or epidural and any deterioration in the cardiotocograph requiring intervention or investigation. These changes are consistent with a previous studies[5,9], but the effects are much less frequent than those observed during systemic administration of other opioids[16]. Reduced beat-to-beat variability has been reported during systemic administration of opioids. Harmer and Rosen pointed out that the significance of reduced beat-to-beat variability during opioid analgesia is uncertain, but that the phenomenon is probably innocent[17].

The neonatal Apgar scores at 1 and 5 min and the neurological examination were within normal limits for all neonates in both groups. The good neonatal outcome is consistent with previous studies, and Apgar scores have been demonstrated to be significantly higher following remifentanil PCA than after meperidine PCA[18]. Fentanyl PCA in labour for those women with a contraindication to epidural analgesia has been shown to be associated with a 44%

incidence of moderately depressed neonates[19].

The mean umbilical cord gases were within normal Range in both groups. Base deficit and lactate measurements are known to correlate significantly and are good indicators of neonatal outcome[20]. These results are similar to those of Volikas et al who studied the maternal and neonatal side effects of remifentanil PCA in labour.

In conclusion epidural infusion gives superior analgesia for labour than PCA remifentanil and that PCA remifentanil is a good, equally safe, and could be alternative method of analgesia for labour. Further studies are needed to evaluate PCA remifetanil for labour analgesia, and to confirm its safety for routine use.

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