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A Randomized Controlled Trial of Intravenous Remifentanil Compared with Intramuscular Meperidine for Pain Relief in Labor

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The aim of this study is to compare the analgesic efficacy and safety of Remifentanil and Meperidineduring an uncomplicated labor, Forty full term parturient with singleton pregnancy and vertex presentation were randomized to receive either Remifentanil (25-50 μg every 4 min, IV) or Meperidine (1 mg kg^{-1}, IM) during active labor and delivery. A Visual Analog Scale (VAS) was used to assess the severity of pain. Also maternal side effects (nausea and vomiting), sedation, perinatal outcome, maternal satisfaction and duration of labor were assessed. The pain scores were lower in Remifentanil group at 60 min after analgesia ($p<0.0001$) and during the first stage of labor ($p<0.0001$) than Meperidine group. The pain scores in second stage of labor were also lower in Remifentanil group ($p = 0/013$). Ninty five percent of women rated analgesia as good to excellent in Remifentanil group as compared with 35% in meperidine group ($p<0.0001$). Side effects such as sedation, nausea and vomiting and respiratory depression and hemoglobin oxygen desaturation were uncommon .Also no significant differences were seen between groups from mode of delivery or neonatal outcomes. Conclusion: Remifentanil with a bolus dose of 25-50 μg offers a good level of maternal satisfaction with a minimal effect on the neonate, but adequate continuous monitoring is necessary for avoiding maternal side effects.

Key words: Remifentanil, Meperidine, analgesia, labor, delivery

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INTRODUCTION

The best regime for labor analgesia has not been established but it will be the regime that results in the best quality of labor analgesia with the least side effects including motor block, using the least amount of drug but is flexible to allow for patient variability. Epidural analgesia offers the best pain relief for many women. If epidural analgesia is contraindicated or a woman does not want to have epidural puncture, opioids are the best alternatives. An optimal analgesic drug for this objective should have potent analgesic efficacy and minimal side effects on mothers and fetus. Recently remifentanil has been evaluated as a better choice of opioid for systemic analgesia. It is a selective mu-agonist. It has an ester linkage which allows the drug to be rapidly metabolized by circulating and tissue esterases. It is an opioid with a rapid onset and offset of effect, which may better complement the intermittent painful contractions of labour. Although it crosses the placenta it is rapidly metabolized and redistributed (Burkle *et al*., 1996). It is hoped that remifentanil should have minimal adverse effects on the neonate (Kan *et al*., 1998). Its major advantage over other opioid is its rapid onset of action (peak effect of 60-80 sec) and a rapid clearance rate. These characteristics should make it an ideal drug for the intermittent painful contractions of labor (Thurlow *et al*., 2002; Glass *et al*., 1993; Selinger *et al*., 1995; Egan *et al*., 1996).

It has been used an IV infusion during nonurgent cesarean section as an adjunct to epidural or general anesthesia (Kan *et al*.,1998; Bedard *et al*., 1999).

Meperidine, a synthetic opioid has been one of the most commonly employed methods so far. When used intramusculary, its analgesic effect starts within 10-20 min and its duration of effect lasts 2-4 h, however some complication such lack of analgesic effect in second stage of labor and neonatal complications were seen with the use of this drug for this aim (Matheson and Nylander, 1999).

The main objective of this investigation was to compare the analgesic effect of IV Remifentanil with IM Meperidine (the routine method in our hospital) as a labor analgesic. In previous studies remifentanil was administered by Patient-Controlled Analgesia (PCA) with a bolus dose of 0.4 μg kg^{-1} (Rabie *et al*., 2006) and a lockout period of 1 min or with a bolus dose of 0.5 μg kg^{-1} (Volikas *et al*., 2005) and a lockout period of 2 min.or) with a bolus dose of 20 μg bolus over 20 sec, 3 min lockout (Thurlow *et al*., 2002). In this study, remifentanil was administered by supervision of an anesthesiologist with a bolus dose of 25-50 μg every 4 min and we have compared the effect of this drug on sedation and maternal satisfaction, duration of the stages of labor and fetal outcomes with intramuscular Meperidine.

MATERIALS AND METHODS

The study included 40 women aged 18 to 40 years of mixed parity with singleton fetus in vertex presentation pregnancies in labor at term, who admitted to the delivery unit of the Ali Ebne Abitaleb hospital in Zahedan within the year 2005. The present prospectively designed study was approved by the ethics and clinical studies committee of Zahedan University of medical sciences and informed and signed consent was obtained from all the patients who were enrolled in the study. The analgesics were infused or injected by the anesthesiologist to the patients, who had a pain score of 6 or more than 6 and were in active labor (3-5 dilatation in cervical examination) and who desired analgesia and had a minimum systolic and diastolic blood pressure 90/60 mm Hg and a minimum pulse rate of 60 min^{-1}.

Exclusion criteria were; women weighting less than 50 kg or more than 100 kg, complicated pregnancy, presence of maternal medical disorders, evidence of cephalopelvic disproportion, uteroplacental insufficiency and drug abuse.

The patients were randomly divided by numbered containers in two groups. After admission to the delivery room, patients were placed in a left lateral position; ringer solution 150 mL h^{-1} was infused. Analgesia was administrated in all the women only in request for pain relief according to the group allocated. With the objective of reducing the incidence of nausea and vomiting, 25 mg Promethazine was administrated intramusculary for all patients. Group 1 (20 cases) were assigned IV Remifentanil via an infusion pump 25-50 μg bolus over 30-60 sec regarding the intensity of the patient's pain and then stopped, permitting a rest time of minimum 4 min. Remifentanil was given at the beginning of a painful contraction.

Group 2 (20 cases) meperidine was administered intramusculary in a dose 1 mg kg^{-1}. The same dose was repeated if subsequent demand was made after 4 h of initial dose. However if a repeat dose was required within 4 h, half of the initial dose was given with a maximum dose of 200 mg. Meperidine administration was stopped once the labor had progressed to 8 cm cervical dilatation. Naloxone was available at the time of delivery. If the assigned analgesia was inadequate for the patients of two groups at any time, an alternative was offered and further study recording were discontinued. Parturient from both

groups were evaluated every 15 min until delivery for the changes in blood pressure, heart rate and respiratory rate, fetal heart rate patterns and symptoms of dizziness, vomiting, fatigue and drowsiness.

The Ramsey sedation score graded between 1 (anxious) and 6 (unarosable), mode of delivery and patient cooperation were recorded. To avoid possible hypoxemia, parturient were also assessed with pulse oximetry and supplemental oxygen was administrated to them whenever SpO_2 decrease to less than 95%.

Pain was assessed by a 10 cm marked visual analog scale (VAS) before analgesic and at 15 min interval until delivery, with zero representing no pain and 10 as the worst pain. For descriptive purpose in second stage, pain score between 0.1-3.9 was taken as mild pain, 4-6.9 as moderate pain, 7-9.9 as severe pain and 10 as intolerable pain.

In addition, patient's satisfaction was assessed after delivery by themselves, using a five point descriptive scale of excellent, very good, good, fair, or poor.

Physiological variables of blood pressure, PR, respiratory rate and episodes of oxygen saturation under 95% were also assessed. Neonatal evaluation was done by a neonatologist blinded to the patients groups using apgar scores and naloxone usage for any presumed opioid induced respiratory depression and other complications were recorded.

Data were analyzed using Mann-whittney-U, Chi-square and Fisher's exact tests, with SPSS 11.0 software. p-value less than 0.05 was considered significant.

RESULTS

Forty women were asked to take part in the study. 20 patients were randomized to each treatment group. The groups did not differ demographically (Table 1). The number of primigravide patients in each group was similar (10/20 in each group). Oxytocin use did not differ between groups. Details of labor in two groups are summarized in Table 2. The pain scores before analgesia and at 60 min and the maximum pain score during the first stage and maternal satisfaction were represented in Table 3 and 4. The mean VAS score at 60 min and maximum pain score during the first stage of labor after analgesia were significantly lower in remifentanil group ($p<0.0001$).

In remifentanil group 65% of women rated analgesia as very good to excellent as compared with 0% of meperidine group ($p<0.0001$). Another 30% in Remifentanil group and 35% in meperidine group considered it to be good. Overall maternal satisfaction (those who rated the analgesia as good to excellent) was 95% of women in remifentanil group and 35% in meperidine group.

Table 1: Patients details before start of analgesia

Variables	Meperidine group (n = 20)	Remifentanil group (n = 20)
Age (year)	25.5±3.1	24.8±2.6
Weight (kg)	70±16	72±11
Height(cm)	156±8.5	157±6.8
Primiparity (percent)	10(50%)	10(50%)
Gestation (week)	38.8±1.2	39.0±7.79
Cervical dilatation (cm)		
At analgesic initiation	3.8±0.8	3.7 ±0.7
Oxytocin use (percent)	7 (35%)	8 (40%)

Results are expressed as Mean±SD or n (%), p>0.05Not significant

Table 2: Duration of the first and second stage of labor in two groups

Characteristics	Meperidine	Remifentanil	p-value
Duration of active stage (h) (mean± SD)	1.95±0.56	2.02± 0.62	NS
Duration of second stage (min) (mean±SD)	26.75± 12.59	39.0±29.09	NS

Table 3: Quality of analgesia (VAS in two groups)

Characteristics	Meperidine	Remifentanil	p-value
Before analgesia	7.8±1.8	7.6±1.4	NS
1 h after analgesia	5.4±0.72	2.35±0.87	0.000
Maximum score over first stage of labor	6.3±1.56	3.3±1.27	0.000

Results are expressed as Mean±SD and n (%)

Table 4: Maternal satisfaction and sedation scores in two groups

Characteristics	Meperidine	Remifentanil	p-value
Maternal satisfaction			
Very good to excellent	0 (0%)	13 (65%)	0.000
Good to excellent	7 (35%)	19 (95%)	0.000
Sedation score			
Less than 3	19 (95%)	19 (95%)	NS
3	1 (5%)	1 (5%)	NS
More than 3	0 (0%)	0 (0%)	NS

Results are expressed as Mean±SD and n (%)

Table 5: Pain characteristic in second stage

VAS	Meperidine	Remifentanil
0 No pain	0 (0%)	0 (0%)
0.1-3.9 mild	0 (0%)	0 (0%)
4-6.9 moderate	11 (55%)	18 (90%)
7-9.9 severe	7 (35%)	2 (10%)
10 intolerable	2 (10%)	0 (0%)
Total	20 (100%)	20 (100%)

Results are expressed as n (%)

In second stage of labor as illustrated in Table 5, sever and intolerable pain were significantly lower in Remifentanil group ($p = 0.013$).

The apgar score at 1 min were ≥ 7 and at 5 min were ≥ 9 in all of neonates in two groups.

There were no significant differences between groups with respect to incidence of nausea and vomiting, systolic and diastolic blood pressure, heart rate and respiratory rate at labor and delivery. For one woman receiving remifentanil hemoglobin oxygen saturation of less than 95% were recorded, resolved by verbal stimulation and hemoglobin desaturation was not seen in any patient in meperidine group. No significant difference was seen between two groups. The cesarean delivery rate was not significantly different between groups.

DISCUSSION

The results of this study indicate that Remifentanil with a bolus dose of 25-50 μg provides better pain relief to mothers during labor and delivery than intramuscular meperidine, judged by VAS pain scores and maternal satisfaction and have minimal side effects.

The assessment of pain relief in labour is not straightforward. The pain experienced is not constant so that what is recordedas the 'worst pain imaginable' (10 cm on a VAS) by a woman in early labour may in fact be less severe than that recorded at 8 cm on a VAS at a later stage. Early retrospective assessment of labour pain (2 h post-delivery) considered with the duration of labour may help solve these difficulties (Ludington and Dexter, 1998) However, in order to assess the efficacy and safety of increasing doses of remifentanil, we recorded VAS scores for pain every15 min during remifentanil use.

The bolus dose range that provides effective analgesia in labour was clearly demonstrated by our study. Bolus doses of 25-50 μg every 4 minutes were responsible for the maximum reduction in pain score in remifentanil group. All women recording either a pain score of fouror less, or those recording the reduction in pain score that they thought to be worthwhile.

Another study (Thurlow *et al*., 2002) compared remifentanil PCA with intramuscular pethidine and found that pain scores were significantly lower with remifentanil. PCA meperidine and remifentanil have recently been compared in labor, but poor apgar scores in the meperidine group terminated the study prematurely (Volikas and Male, 2001).

When PCA remifentanil was compared with IM meperidine (Volmanen *et al*., 2002) the pain scores were lower in remifentanil group and the respiratory depression effect was greater. In our study, an anesthesiologist administrated remifentanil by an infusion pump and meperidine was given in a limited dose to the patients to avoid excessive sedation and others side effects.

In our study there was a small rate of sedation and minimal respiratory and cardiovascular depression in both groups.

How was the doses of remifentanil chosen:Volmanen *et al.* (2005) in their study with remifentanil PCA in 17 labouring women reported that the bolus dose of 0.4 μg kg^{-1} (range 0.2-0.8 μg kg^{-1}) with median consumption 0.066 μg kg^{-1} min^{-1} (range 0.027-0.207 μg kg^{-1} min^{-1}) with a 1 min lockout administered in a time of one minute is effective. In their study, in 10 of the 17 women desaturation episodes (pulse oximetry reading <94%) were recorded between contractions. These desaturations either resolved spontaneously or by deep inspirations. So they concluded that, remifentanil is a potent respiratory depressant and adequate continuous monitoring is necessary.

So we must remember that another concern with remifentanilremains the threat of maternal respiratory depression, but both with remifentanil and pethidine, episodes of desaturation can occur. (Blair *et al*., 2005, Evron *et al*., 2005).

In this present study the bolus dose of remifentanil administrated was limited to 50 μg. Ideally an intermittent incremental regimen with starting bolus of 20 μg irrespective of the parturient's weight and increasing the bolus dose slowly over time, may be more effective (Shmuel *et al*., 2005).

Remifentanil when administrated with PCA without background infusion provided safe but incomplete analgesia (Blair *et al*., 2001). The fact that painful contractions in labor are normally intermittent and remifentanil is an ultra short acting drug, it is inappropriate to apply continuous analgesia.

With respect to fetal or neonatal side effects, Remifentanil was associated with fewer abnormalities of the fetal Apgar score; this could be explained by the shorter duration of the drug action (Shmuel *et al*., 2005) but there is also a few case reports and small series with contradictory results (Olufolabi *et al*., 2000). In our study neonatal outcomes was good and similar in both groups.

Also in our study, there were stable hemodynamic parameters in both groups and episodes of desaturation was uncommon in two groups (only one patient in remifentanil group and no patient in meperidine group).

The incidence of cesarean delivery rate was not significantly different between groups. First stage of labor was not prolonged in both groups and prolongation of second stage was not significantly different between groups ($p = 0.09$). Our sample size was small and a larger study is necessary to investigate it and other maternal and fetal side effects.

In conclusion, remifentanil with a bolus dose in the range 25-50 μg every 4 min appears a safe and effective drug for use in labour when epidural analgesia is unsuitable; however adequate continuous monitoring is advisable.

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