LABOR ANALGESIA IN PREECLAMPSIA: REMIFENTANIL PATIENT CONTROLLED INTRAVENOUS ANALGESIA VERSUS EPIDURAL ANALGESIA

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Abstract

Background: Epidural analgesia is considered to be the preferred method of labor analgesia in preeclamptic patients. Systemic opioids are another good effective, easy to administer alternative but may cause maternal and fetal respiratory depression. Remifentanil's rapid onset and offset of effects, should make it an ideal drug for the intermittent painful contraction during labor. *Method:* 30 preeclamptic patients were randomly assigned to one of two equal groups; **Epidural Group:** received epidural analgesia according to a standardized protocol using bupivacaine plus fentanyl. **Remifentanil Group:** PCA was set up to deliver remlfentanil 0.5 µg/kg as a loading bolus infused over 20 seconds, lockout time of 5 minutes, PCA bolus of 0.25 µg/kg, continuous background infusion of 0.05 µg/kg/min, and maximum dose is 3 mg in 4 hours. Women were advised to start the PCA bolus when they feel the signs of a coming uterine contraction. *Results:* All women demonstrated a significant decrease in VAS score in the first hour after administration of analgesia ($P<0.05$). Analgesic quality as regard Visual Analog Pain Scores, sedation score, and post-delivery patient satisfaction in both groups, are comparable ($P>0.05$). PCA remifentanil infusion until time of delivery produce no observable maternal, fetal or neonatal side effects ($P<0.05$).

Conclusion: PCA intravenous remifentanil is an effective option for pain relief with minimal maternal and neonatal side effects in labor for preeclamptic patients with contraindications to epidural analgesia or requesting opioid analgesia.

Keywords: Preeclampsia, PCA remifentanil, epidural, labor analgesia.

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Introduction

The goal of labor pain relief for pre-eclamptic parturients is to provide the most effective analgesia in order to reduce stimulation of the sympathetic nervous system[1,2].

Epidural analgesia was proven safe for use in such patients[3] and particularly beneficial to the mother and baby as it prevents the exacerbation of hypertension and improve uteroplacental circulation.[4] The anesthesiologist concerns with epidurals stem from the episodes of hypotension, predisposition of preeclamptic patients to develop pulmonary edema[4], and coagulopathies. The latter interfering with the ability to provide neuraxial anesthesia[5]; hematoma formation[6,7] spinal cord compression and permanent paralysis. Disturbances of platelet counts, platelet function or disseminated intravascular coagulation can also increase the risk for excessive bleeding. Coagulopathy, anesthetists are concerned about epidural.

On the other hand systemic opioids are the most common form of labor analgesia worldwide and when administered by the proper delivery system, can also be the second most efficacious form of pain relief[2]. Intramuscularly administered narcotics is a poor method of drug delivery for labor pain as the relatively slow absorption leads to fluctuating peaks and troughs in serum levels[8]. This method of administration also is painful and is contraindicated when the patient is thrombocytopenic (<50000-75000 platelets)[2].

The intravenous administration of narcotics is the best method of administration for labor pain. Ideally, the patient controlled analgesia (PCA) system is available to these women. The particular narcotics used in this system include morphine, fentanyl, meperidine, nalbuphine, and alfentanil[9]. The ideal agent of choice is a short-acting narcotic that does not accumulate over time and has a large therapeutic/ toxic plasma ratio. Regardless of the narcotic chosen, particular monitoring requirements must be in place to avoid potential maternal and neonatal complications[2]. Therefore, the minimum requirements of monitoring for the mother during administration consist of an hourly respiratory rate and sedation score used for normal labour.

Meperidine the most commonly used for labor pain is associated with a high incidence of maternal nausea and sedation, as well as many adverse fetal and neonatal effects[10].

The use of intravenous patient controlled analgesia (PCA) with fentanyl has been associated with up to a 44% incidence of moderately depressed neonates with low Apgar scores[11]. Moreover, fentanyl does not always provide adequate pain relief for the intense pain of the late first stage of labor, most likely due to its slow onset of action[12]. A search for a new opioid to overcome these problems has led to the introduction of remifentanil for labor analgesia[13,14,15].

Remifentanil has a unique pharmacokinetic profile, with a potent ultra-short μ opioid receptor agonist action. The metabolism of remifentanil is independent of renal and hepatic function. It has rapid onset (time to peak effect 60 to 80 sec) and offset times, irrespective of the duration of administration[16]. The drug's context sensitive half-time is three minutes[17]. Remifentanil rapidly crosses the placenta but is quickly redistributed and metabolized in the fetus[18,19]. There have been no reports of associated increases in neonatal respiratory depression or lower Apgar scores with the use of remifentanil prior to delivery. With these properties, remifentanil appears to be the opioid of choice for labor, since it can be appropriately titrated for administration when analgesia is required for either very brief or prolonged periods, without the concern of prolonged recovery. It therefore resembles the description of an ideal systemic analgesic for use during labor.

To the best of our knowledge, no trial as yet been carried out, to study the efficacy of using remifentanil patient controlled analgesia for the pain management in preeclamptic patients. This study was planned to compare the use of remifentanil PCA intravenous analgesia to epidural bupivacaine plus fentanyl for labor analgesia in preeclamptic patients.

Material and Methods

After having patient informed consent, thirty nulliparous preeclamptic parturient were studied. Patients were recruited during early first stage of labor before requesting pain relief were studied. Inclusion criteria consisted of; ≥32 weeks gestation, normal cephalic presentation, <5 cm cervical dilatation,

clinical diagnosis of preeclampsia. Which required at least one of the following three criteria:

1) Systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg, with proteinuria of 1 + on dipstick.

2) Systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg with proteinuria of 2 + or more on dipstick.

3) Systolic blood pressure greater than or equal to 160 mmHg or diastolic blood pressure greater than or equal to 110 mmHg with proteinuria of either 2 + on dipstick.

Exclusion criteria were consisted of; remifentanil allergy, progression to eclampsia, evidence of increased intracranial pressure or focal neurologic deficit, Women with a platelet count of less than $80 \times 10^9/L$, or evidence of pulmonary edema, nonreassuring fetal heart rate tracing requiring imminent delivery.

After arriving to delivery suit, an 18 G intravenous cannula was established and lactated Ringer's solution at a rate of 100 ml/hour was given to all parturients. Intravenous magnesium sulfate for seizure prophylaxis from the diagnosis of preeclampsia until 24 hours postpartum was given when instructed by the obstetrician. The standard magnesium sulfate regimen is a 4g intravenous bolus given over 20 minutes, followed by a continuous infusion of 2 g per hour. After proper explanation of both techniques patients were randomly assigned to one of two groups. (15 each)

Epidural Group: Following lumbar epidural according to a standardized protocol, on epidural catheter was placed under complete aseptic technique at the L3-L4 or L4-L5 interspaces. A test dose of 3 mL of 0.25% bupivacaine was administered, and epidural analgesia was established with initial bolus of 10-15 mL of 0.25% bupivacaine plus 1 μg/kg fentanyl. Analgesia was maintained by continuous infusion of 0.125 bupivacaine plus 2 μg/ml fentanyl at a rate of 10-12 ml per hour aiming to obtain a T-10 sensory level.

Remifentanil Group: Patients were first introduced to the proper use of the PCA pump (Grasby 3300). A dedicated intravenous cannula was sited for remifentanil delivery and the Remifentanil hydrochloride concentration used was 50 μg/ml (3 mg diluted to 60 ml of normal saline).

The PCA was set to deliver 0.5 μg/kg as a loading bolus infused over 20 seconds, lockout time of 5 minutes, PCA bolus of 0.25 μg/kg, continuous background infusion of 0.05 μg/kg/min, and maximum dose is 3 mg in 4 hours. Women were advised to start the PCA bolus when they feel the signs of a coming uterine contraction.

Oxygen saturation (SpO_2), Heart rate (HR), Blood pressure (Bp), and Respiratory rate (RR) were monitored continuously and recorded every 5 minutes.

Hypotension, (defined as reduction of >25% of baseline level), was treated by either additional intravenous crystalloid or intravenous bolus doses (e.g., 2.5-5.0 mg) of ephedrine. Reductions in blood pressure of less than 25% in the presence of a reassuring fetal heart rate tracing (as determined by the managing obstetrician) were not treated. If the assigned analgesia was inadequate for the patient at any time, an alternative was offered and further study recording were discontinued.

For hourly pain assessment and a visual analogue pain score (0 marked no pain and 10 marked worst pain) was obtained and recorded at three data points before analgesia, one hour after, and after delivery. Satisfactory analgesia is considered if VAS is ≤ 3. Hourly Sedation score was assessed and recorded at the same data points using a four point scale (1= alert, 2= slightly drowsy, 3= drowsy not responding to gentle stimulation, 4= very drowsy). Overall patient satisfaction were determined within 24 hours of delivery (1: poor, 2: fair, 3: good, 4: excellent). Requirement for pharmacologic interventions to treat hypotension and the incidence of complications were recorded.

Continuous cardiotocogram monitoring of fetal heart rate uterine contraction were used and analyzed by the obstetrician. Neonatal data included birth weight, Apgar scores at 1 and 5 minutes, umbilical cord arterial blood gas results, naloxone treatment, neonatal intensive care admission. Any morbidities and mortalities were recorded.

Statistical Analysis

Demographic data were analyzed with unpaired Student's t test. Paired Student's t test was used to compare values in the same group. One way and two ways ANOVA were used for within and between groups comparisons of Maternal hemodynamics. Maternal visual analog score, and sedation score, between groups were compared using Kruskal-Wallis ANOVA test and Friedman two-way ANOVA for within group analysis. Maternal visual satisfaction score was compared using Mann-Whitney test. Maternal side effects and fetal side effects were analyzed using Chi-squared test. All statistical analysis was performed using Excel and SBSS statistical packages.

Results

Demographic Data

Both groups were matches for Age, Weight, Height, Gestational age, Baseline cervical dilatation, and baseline lab results (P>0.05). Incidence of instrumental delivery and cesarean section was higher in Epidural group compared to the Remifentanil one (P<0.05). (Table 1)

Table 1
Demographic Data and Type of delivery
(mean ± SD or numbers)

Variable	Epidural Group (n = 15)	Remifentanil Group (n = 15)
Age (year)	26 ± 8	28 ± 9
Weight (Kg)	79 ± 22	84 ± 37
Height (cm)	163 ± 6	162 ± 7
Gestation (week)	36 ± 4	35 ± 3
Cervical Dilatation (cm)	3.2 ± 1.4	3.4 ± 1.5
Baseline lab. Results • Platelet count (× 10⁹/L) • Serum Creatinine (mg/dL)	175 ± 63 0.8 ± 0.3	178 ± 55 0.8 ± 0.25
Type of delivery • Normal delivery • Instrumental Delivery • Cesarean Section	8* 3* 4*	10 0 3

* Significant difference compared to remifentanil group

Maternal vital signs:

The two groups were comparable with respect to maternal hemodynamic in the means of; SBP, HR, SpO_2, and Respiratory Rate. Data were analyzed at three points before starting analgesia (baseline), 1 hour after starting analgesia, and after delivery (Table 2).

Table 2
Changes in the mean Systolic Blood pressure before starting analgesia (baseline), 1 hour after starting analgesia, and after delivery. Values are mean ± SD

	Baseline	1 hr after analgesia	After delivery

Mean BP (mmHg)
  - Epidural group
  - Remifentanil group
	99.4 ± 13
	100.5 ± 6.9
		95 ± 8.7
		96.2 ± 6.6
			97.7 ± 7.6
			99 ± 9

Mean HR (beat/min)
  - Epidural group
  - Remifentanil group
	80.6 ± 10.8
	81.2 ± 11.2
		81 ± 7
		79.2 ± 10.3
			79.8 ± 10.4
			80.1 ± 8.4

Mean SpO_2 (%)
  - Epidural group
  - Remifentanil group
	98.2 ± 1.4
	98.4 ± 1.3
		97.8 ± 1.9
		97.5 ± 1.5
			97.3 ± 1.9
			97.8 ± 1.5

Mean Respiratory rate - Epidural group - Remifentanil group	18.3 ± 3.4 18.5 ± 3.4	17.5 ± 3.4 17.8 ± 2.4	17.2 ± 3.1 17.5 ± 2.6

Quality of analgesia

Maternal pain score, sedation score, and post delivery satisfaction:

Maternal Visual Analog Pain Score (VAPS) and Sedation scores were assessed before starting analgesia (baseline), 1 hour after starting analgesia, and after delivery. There were no inter-group differences in the VAS or sedation scores at the three times measured (P>0.05). Within group analysis revealed significant decreased in VAS after starting the analgesia in both groups (Table 3). In the PCA intravenous Remifentanil group, the patient satisfaction was better than in the epidural group although it is was statistically insignificant. (P>0.05)

Table 3

*Changes in the mean Maternal Visual Analog Pain Scale,
mean Sedation score (VAS) at baseline, 1 hour after analgesia,
and after delivery and patient satisfaction*

Values are mean ± SD

	Epidural Group (n = 15)	Remifentanil Group (n = 15)
Pain VAS Score • Baseline • 1 hr after • After delivery	8 ± 1.7 2.6 ± 1.5 3 ± 1.4	7.9 ± 1.7 3 ± 1 2.8 ± 1.1
Sedation Score (1-4) • Baseline • 1 hr after • After delivery	1 ± 0.25 1.1 ± 0.35 1.06 ± 0.25	1 1.3 ± 0.48 1.1 ± 0.35
Patient Satisfaction Score (1-4)	2.8 ± 1	3.1 ± 0.9

Table 4

The number of maternal side effects in the two groups.

Values are number (%)

Side Effects	Epidural Group (n = 15)	Remifentanil Group (n = 15)
Nausea	7 (46.6%)	5 (33%)
Vomiting	2 (13.3%)	1 (6.6%)
Itching	3 (20%)*	1 (6.6%)
Hypotension	4 (26.6%)*	0 (0%)

Table 5

Incidence of fetal and neonatal side effects.

Value are numbers (%)

	Epidural Group (n = 15)	Remifentanil Group (n = 15)
FHR abnormalities at one hour after analgesia	2 (13.3%) *	0 (0%)
Apgar Score ≤7 • 1-minute • 5-minutes	1 (6.6%) 0 (0%)	1 (6.6%) 0 (0%)
Naloxone	2 (13.3%)*	0 (0%)
Umblical cord gas • Umblical artery pH • Umblical vein pH	7.24 ± 0.09 7.3 ± 0.03	7.23 ± 0.07 7.32 ± 0.03
Seizure	0 (0%)	0 (0%)
Mechanical ventilation	2 (13.3%)*	0 (0%)

* Significant difference compared to remifentanil group

Maternal Side effects

Nausea, and or vomiting in the epidural group was higher than in remifentanil group but still statistically insignificant ($P>0.05$). Itching and hypotension that necessitated pharmacological interventions, were statistically significantly higher in epidural group than remifentanil group ($P<0.05$)

Fetal and neonatal outcome

Fetal heart rate abnormalities (fetal heart rate deceleration to < 90 beats/min or late deceleration) were recorded one hour after start of analgesia, in both groups (Table 5). Two patients in epidural group developed fetal heart rate abnormalities compared to no patients in remifentanil group. Incidence of mechanical ventilation, naloxone used was statistically significant in epidural group compared with the remifentanil one ($P<0.05$). There were no differences between the neonates in the two groups as regard the APGAR score measured at the two different times. Also no statistically significant difference between groups as regard seizure or umbilical cord blood gases analysis ($P>0.05$).

Discussion

The chief role of the anesthesiologists is to provide safe labor analgesia[20], the choice, however, of the optimum technique in preeclamptic patients is controversial[21,22]. The results of this study indicate that PCA remifentanil for preeclamptic patients during labor and delivery is associated with a decrease in VAS pain score, acceptable sedation score, and good patient satisfaction that is comparable to the epidural technique. The maternal, fetal, and neonatal side effects in remifentanil group were minimal and rapidly resolved due to short duration of action and lack of accumulation of remifentanil.

There were no significant differences in the maternal vital signs (SBP, HR, SpO_2), or respiratory rate (RR) between the two groups in the doses used, indicating minimal or no serious side effects on the mother by the use of either epidural bupivacaine-fentanyl, or intravenous remifentanil.

Maternal side effects (Nausea, vomiting, itching, and hypotension), were lower in remifentanil group compared to epidural group but was statistically

significant in case of itching, hypotension, and the rate of instrumental and cesarean section delivery (P<0.05). Some studies found significantly greater requirements for ephedrine in women with severe preeclampsia who received epidural analgesia[4,23]. Although, maternal side effects were not observed in our study, but its potential it like any opioid analgesia, a well-trained staff therefore is recommended for close observations.

The continuous remifentanil infusion until the time of delivery produced no observable fetal or neonatal side effects compared to the epidural group, (P>0.05). This was indicated by the normal Apgar score, reassuring fetal heart rate tracing, normal umbilical cord gases, the absence of need for naloxone, or mechanical ventilation for the neonates. This is attributable to the assumption that remifentanil crossed the placenta was either rapidly metabolized or redistributed in the neonates causing no adverse effects.

Our findings of an absence of any fetal or neonatal adverse effects are consistent with other studies[13,14,15,24]. Other findings are in contradictory[25,26,27] with respect to maternal and neonatal side effects, which can be explained by the various doses used and mode of administrations.

The short duration of action and the lack of accumulation of remifentanil resulted in rapid spontaneous resolution of any side effects. Whereas the significant FHR abnormalities in the epidural group is similar to the findings of other study[28], comparing normotensive women with epidural analgesia, women with hypertension and epidural analgesia had a three-fold increased risk of ominous fetal heart rate tracings.

All women demonstrated a significant decrease in VAS score in the first hour after administration of analgesia (P<0.05), denoting effective analgesia in both groups. Comparison of the analgesic quality of the Visual Analog Pain Scores, sedation score, and post-delivery patient satisfaction between the two groups,

show comparable analgesic efficacy of both techniques (P>0.05). This suggests that remifentanil may have a true analgesic effect on labor pain, an effect consistent with many previous studies[8,24].

A variety of doses and delivery systems have been previously[8,9,15,29] for the purpose of identifying an efficient and safe approach of remifentanil administration. The concomitant use of a background infusion is controversial[30]. Some studies recommended the use of a background infusion[31], and others argued that remifentanil administration without a background provides safe but incomplete analgesia[13]. Because of the fact that it is difficult, to coincide the peak effect of remifentanil with each uterine contraction but with the subsequent contraction[32], a background infusion was chosen in this study to provide constant baseline analgesia and that only the contraction peaks required treatment with rescue boluses. Our regimen results was compared with similar one[31] used resulted in effective analgesia with a rate of conversion to regional analgesia of 5%, which is the lowest reported to date.

With the PCA intravenous remifentanil used in this study, the patient benefits from a greater sense of control over her pain management, plus the anxiolytic effect of using narcotic (remifentanil), which is an important psychological effect that contributes to the success of this technique. Remifentanil reduces pain during labor and does not cause immediate or prolonged hazards to mother or fetus.

Conclusion

PCA intravenous remifentanil is an effective option for pain relief with minimal maternal and neonatal side effects in labor for preeclamptic patients with contraindications to epidural analgesia or requesting opioid analgesia. Further studies in larger population of preeclamptic patients are recommended to ensure the safety of this regimen.

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