# Bupivacaine with Meperidine versus Bupivacaine with Fentanyl for continuous epidural labor analgesia

*Islam M. Massad,* MD, *Maysa M. Khadra,* MD, *Fawaz A. Alkazaleh,* MD, *Ayman M. Qatawneh,* MD, *Shawqi S. Saleh,* MD, MRCOG, *Sami A. Abu-Halaweh,* MD, FFARCSI.

## ABSTRACT

**Objective:** To compare the efficacy of bupivacaine-meperidine and bupivacaine-fentanyl mixtures when continuously infused epidurally to relief the labor pain.

**Methods:** We performed this prospective double-blinded study at Jordan University Hospital, Amman, Jordan between October 2005 and April 2006. Sixty-seven American Society of Anesthesia physical status I parturients were randomly divided into 2 groups, Group M (n=34) received a continuous infusion of 1 mg/ml of bupivacaine mixed with 1 mg/ml meperidine, and Group F (n=33) received a continuous infusion of 1 mg/ml bupivacaine mixed with 2 µg/ml fentanyl. Efficacy of analgesia, degree of motor block, hemodynamic variability, incidence of nausea and vomiting, pruritus, sedation, and the neonatal outcome were all compared between the 2 groups. A p value <0.05 was considered to be significant.

**Results:** Highly effective analgesia was achieved in both groups with a similar incidence of motor block, sedation, pruritus, and neonatal outcome. The only significant difference was in the incidence of nausea and vomiting. Group M had 8 parturients with nausea, compared with only 2 parturients in Group F ($p$=0.003).

**Conclusion:** Bupivacaine-meperidine in a continuous epidural infusion is as efficient as bupivacaine-fentanyl for pain relief during labor, but associated with a higher incidence of nausea and vomiting.

***Saudi Med J 2007; Vol. 28 (6): 904-908***

*From the Department of General Surgery Anesthesia and Intensive Care (Massad, Halaweh) and the Department of Gynecology and Obstetric (Khadra, Alkazaleh, Qatawneh, Saleh), University of Jordan, Jordan University Hospital, Amman, Jordan.*

*Received 7th November 2006. Accepted 10th January 2007.*

*Address correspondence and reprint request to: Dr. Islam M. Massad, Department of General Surgery, Anesthesia and Intensive Care, University of Jordan, Jordan University Hospital, PO Box 13046, Amman, Jordan. Tel. +962 (6) 5353666 Ext. 2420. Fax. +962 (6) 5823684. E-mail: islam_wafa@yahoo.com*

Although systemically administered meperidine is still the most widely used opioid for the treatment of labor pain, its use nowadays is questionable because of its minimal effectiveness and significant adverse effects on the mother and the baby.[1,2] Meperidine is an effective epidural opioid[3] and its use alone or in combination with local anesthetics was proved over 20 years ago;[4,5] despite being associated with a number of side effects including mild sedation, pruritus, nausea and vomiting to hemodynamic instability.[4] The administration of a mixture of an analgesic with a local anesthetic in continuous infusion through the epidural route is a popular epidural technique; since it provides the advantages of satisfactory analgesia, lowers the side effects of each drug, and decreases the problems of hemodynamic instability of the therapeutic mixture. This technique was not common in the obstetric practice in the early eighties of the last century, when morphine and meperidine were the standard narcotics administered epidurally in labor and before the widespread use of the lipid soluble opioid such as fentanyl or sufentanyl. Because meperidine has an intermediate lipid solubility, it has an advantage over fentanyl in causing less systemic absorption, and over morphine in causing less rostral movement in the epidural space.[3] Therefore, we evaluated the efficacy of epidural meperidine in combination with bupivacaine used in labor when continuously infused in terms for pain relief, associated motor block, fetal well-being, and side effects, in comparison with our standard epidural technique of bupivacaine-fentanyl.

**Methods.** Following scientific committee and Institutional Review Board (IRB) approval, an informed written consent was obtained from 67 American Society of Anesthesia (ASA) physical status I obstetric patients who had requested epidural labor analgesia in the labor room of the



14Bupivacaine20061297.indd 904 5/15/07 10:17:05 AM

Jordan University Hospital, The University of Jordan, Amman, Jordan, between October 2005 and April 2006.

Inclusion criteria included patients in active labor, at >36 weeks gestation, cervical dilatation ≤5 cm, single fetus, vertex presentation with normal heart rate tracing. Patients were excluded if they had received any kind of analgesia before epidural injection, physical status ASA ≥2, maternal age <18 years, if there was a contraindication for fentanyl, meperidine, or bupivacaine, if delivery is expected within 60 minutes of epidural catheter insertion, if the parturients were hypertensive, or if the patient received any opioid during labor before initiation of epidural analgesia. Following the intravenous administration of 500 ml of a lactated ringers solution, documentation of patients' blood pressure as well as assessment of the lower limb motor function were carried out. We assessed the patients by asking them about the presence of symptoms such as purities, nausea and vomiting. The baseline assessment of pain was carried out using the visual analog scale (VAS) using the 100 mm line, with 0 representing no pain and 100 being the worst possible pain. Epidural catheter placement was performed while the patients in sitting position, at L2-L3 or L3-L4 interspaces using the loss-of-resistance-to-saline technique and the catheter was inserted approximately 4-5 cm into the epidural space (Perifix® epidural set B-Braun, Melsungen AG, Germany). The patients were then randomized into one of 2 groups according to sealed opaque envelopes. An anesthesiologist not involved in the data collection opened the envelopes. One of 2 preparations was then prepared and administered a bolus dose of 10 mg meperidine mixed with 10 mg bupivacaine in a total volume of 10 ml of 0.9% saline, followed by a continuous administration of a solution of meperidine 1 mg/ml with bupivacaine 1 mg/ml (Group M) or a bolus dose of 20 µg fentanyl mixed with 10 mg bupivacaine in a total volume of 10 ml of 0.9% saline, followed by a continuous administration of a solution of fentanyl 2 µg/ml mixed with bupivacaine 1 mg/ml (Group F). Epidural catheters were inserted for included patients only on request for pain relief during active labor, boluses followed by continues infusion were started immediately after the catheter insertion. The infusion rate of both preparations was 15 ml/hr (LIFECARE®5000 Infusion system; Abbott Laboratories, North Chicago, USA), the anesthetist, nurses, obstetrician in charge and the patients were all blinded to the preparations. The doses for the 2 mixtures were made sure to be equipotent.[6] The study ended at the time of vaginal delivery; assisted or not, or when the decision was made to perform cesarean delivery. Assessment of pain by VAS after drug administration was at regular intervals every 30 minutes. If inadequate pain relief was described, an additional analgesia (10 ml of the mixture) was injected through the epidural catheter and was repeated and recorded until the patient feels comfortable. Motor block (Modified Bromage score: 0 = ability to move hip, ankles, and knees; 1= inability to raise extended leg; 2 = inability to flex the knee; 3 = inability to flex ankle, foot or knee), sedation (0 = no sedation, 1 = response to verbal stimuli, 2 = response to painful stimuli, 3 = coma), nausea and vomiting, and pruritus were all documented every 30 minutes by simply asking the patient about their presence. Blood pressure was measured every 5 minutes until 30 minutes after the bolus administration, and then every 15 minutes till the end of the study. Hypotension defined as a decrease in the systolic blood pressure below 90 mmHg, was planned to be managed with left uterine displacement, accelerating intravenous fluid administration, or with a 3-6 mg intravenous bolus of ephedrine. Fetal well-being was monitored continuously throughout labor by using a cardiotocography, Apgar scores at 1 and 5 minutes, birth weight, admission to the Neonatal Intensive Care (NICU), and neonatal complications were all documented. The primary outcome variable was pain assessed by VAS, which was compared between the 2 groups.

***Statistical analyses.*** All the results were expressed as mean, and standard deviation. Analysis of variance (ANOVA) and t-test analysis were used to compare the means of the 2 groups. A p value <0.05 was considered significant. All statistical analysis was carried out using Statgraphics plus 5.1 (Manugistics®, USA). Graphs and tables were prepared using Graphpad Prism software (USA).

**Results.** Sixty-seven patients agreed to participate in the study, where 33 patients received bupivacaine-fentanyl (Group F) and 34 patients received bupivacaine-meperidine (Group M). The analysis of the data of the enrolled patients showed that the 2 groups were comparable with regard to age, body mass index, parity, gestational age, and cervical dilatation at the time of catheter placement (**Table 1**). The pre-analgesic mean VAS scores were comparable in the 2 groups, the mean score was 56 ± 22 for Group F and 57 ± 26 for Group M; probability values were not statistically significant . After administering the analgesic drugs, and when compared with the baseline, the pain relief in both studied groups improved significantly. The mean VAS was 23 ± 22 for Group F ($p$=0.0001) and 24 ± 25 for Group M ($p$=0.0001). Comparing the difference between the 2 groups for all the registered time intervals did not show any significant differences, and it continued to be so until the end of the study (**Figure 1**). During



14Bupivacaine20061297.indd 905 5/15/07 10:17:06 AM

**Table 1 -** Demographic and obstetric data.

| Parameter | Group F ( n=33 ) | Group M ( n=34 ) |
|---|---|---|
| Age ( years) | 29 ± 7 | 28 ± 6 |
| Body mass index (kg/m²) | 28.1 ± 0.6 | 28.4 ± 0.5 |
| *Parity (n)* | | |
| Para 0 and 1 | 20 | 23 |
| More than 1 | 13 | 11 |
| Cervical dilatation at time of initiation of epidural analgesia (cm) | 3.2 ± 1.1 | 3.7 ± 1.0 |
| Gestational age (week) | 39 ± 1 | 39 ± 2 |

Data are expressed as number of patient per group or mean ± SD. There was no significant difference between the groups. Group F - Bupivacaine-Fentanyl group. Group M=Bupivacaine-Meperidine group.

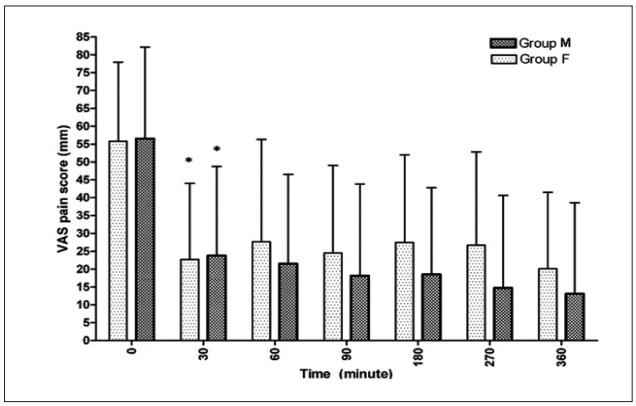


**Figure 1 -** Visual analog scale (VAS) pain scores in Group M and Group F throughout measurement periods (0-360 minutes). Pain scores dropped significantly after the bolus dose in both groups (p<0.0001) and continued with comparable low VAS scores at all other time intervals. Mean and standard deviation are shown.

**Table 2 -** Pruritus, nausea and vomiting, sedation, Motor Block, and extra boluses needed.

| Parameter | Group F ( n=33 ) | Group M ( n=34 ) |
|---|---|---|
| Pruritus | 1 (3) | 1 (2.9) |
| Nausea and vomiting | 4 (12) | 8 (23.5)* |
| ***Simple sedation scale score*** | | |
| 0 | 22 (66.7) | 26 (76.5) |
| 1 | 11 (33.3) | 7 (24.5) |
| 2 or 3 | 0 | 0 |
| Motor block | 7 (21.2) | 5 (14.7) |
| Patients received extra boluses | 7 (21.2) | 6 (17.6) |

Data shown are number of patient per group and percentage of the population. *Significant difference ($p$<0.05), Group F - Bupivacaine-Fentanyl group. Group M - Bupivacaine-Meperidine group.

**Table 3 -** Neonatal outcome.

| Parameter | Group F ( n=33 ) | Group M ( n=34 ) |
|---|---|---|
| Birth Weight (kg) | 3.1 ±0.1 | 3.1 ±0.1 |
| Apgar Score <7 at 1 minutes | 1 (3) | 2 (5.9) |
| Apgar Score <7 at 5 minutes | 1 (3) | 2 (5.9) |
| NICU admission | 2 (6.1) | 5 (14.8) |

Data shown are number of patient per group and percentage of the population. Birth weight is expressed as mean ± SD, Group F - Bupivacaine-Fentanyl group. Group M - Bupivacaine-Meperidine group. NICU - Neonatal Intensive care Unit.

the entire study period, there were no statistically significant difference in the number of the patients who required additional boluses for inadequate pain relief or those who experienced some degree of motor block (Bromage 1 or 2) at one or more time during labor (**Table 2**). The only significant difference between the 2 groups was the incidence of nausea and vomiting. Four parturients (12%) in Group F and 8 in Group M (23.5%) experienced attacks of nausea and vomiting ($p$=0.003). Occurrence of other side effects such as pruritus, and sedation was similar in the 2 groups (p values were not considered significant) (**Table 2**). The hemodynamic status also did not differ in the 2 groups and none of the parturients needed any treatment ( data not shown). The mean birth weight of neonates was similar in both groups (3.1 kg ± 0.1) And the Apgar scores at 1 and 5 minutes were also comparable with no significant differences (p values were not considered significant) (**Table 3**). The neonatal admissions to the NICU were 5 (14.8%) in Group M, and 2 (6.1%) for group F (6.1%) (**Table 3**). Two cases were admitted to the NICU due to prolonged premature rupture of the membranes (PROM), one admitted patient had mega ureter, one neonate had Spina bifida, and one patient had intrauterine growth retardation (IUGR) in Group M, while in Group F the 2 patients had intrauterine growth retardation (IUGR). Although this difference looks important, it did not reach statistical difference (**Table 3**).

**Discussion.** The efficacy of meperidine mixed with bupivacaine for continuous epidural infusion in labor has not been established before; nevertheless, large fractional boluses of epidural meperidine gained particular popularity in obstetrical practice in the past before the widespread use of the lipid soluble opioid.[4,5,7] Recently, meperidine has been used for post cesarean section analgesia.[8] The studies describing the administration of epidural meperidine alone[5,7,8] or when



14Bupivacaine20061297.indd 906 5/15/07 10:17:07 AM

mixed with the local anesthetic bupivacaine,[4] showed adequate pain relief with good patient satisfaction. The side effects due to the relatively high fractional doses of meperidine needed to relief labor pain were significant; ranging from sedation, drowsiness, nausea, to hemodynamic instability and negative effects on the baby due to high placental transfer. When the new generation opioids became the standard in this era, the continuous infusion technique became also the standard technique of drug administration for epidural mixtures in labor, so meperidine administration with local anesthetic in continuous infusion was not tried. Another issue is that most anesthesiologists have a belief that other drugs such as sufentanyl and fentanyl are the drugs of choice for this purpose; despite these drugs being lipid soluble, which might allow for being absorbed systematically to a larger degree; a point to consider when weighing the advantages between parental administration of these drugs and the epidural route. The infusion of a mixture of a local anesthetic with an analgesic is considered the standard technique of epidural administration in labor nowadays, because it results in a greater patient satisfaction, better analgesic efficacy, and less motor block when compared with local anesthetic administration alone.[9-11] The motor blocks in our both studied groups were similar with no statistical difference (7 in group F and 6 in Group M). The motor block might be due to the administration of a relatively high dose of local anesthetic (10 mg loading, 15 mg/hr maintenance of bupivacaine), rather than a direct effect of the administered opioid. This hypothesis is supported by evidence that smaller doses of local anesthetic were given with a higher fentanyl dose to achieve a walking epidural analgesia,[12] a technique that is gaining more popularity and research interest nowadays. Our data also shows that although meperidine has local anesthetic activity, it did not increase the motor block incidence; a finding that might be due to the small meperidine dose we used. Other potential side effects of continuously administered opioid are sedation and pruritus. For intrathecally given opioids, a dose response relationship between lipid solubility and side effects such as sedation and pruritus is well known.[13] Since fentanyl is known to have more lipid solubility than meperidine; fentanyl is expected to cause more sedation and pruritus than meperidine in equipotent doses, yet our both studied groups were similar in that manner with no difference in the incidence of sedation and pruritus. Only one patient in each group had pruritus, and there was a non-significant difference in sedation incidence in the 2 groups. Despite the fact that meperidine has additive local anesthetic activity, the hemodynamic changes are very minimal.[14] This was seen in our study and neither one of the mixtures caused any hemodynamic instability; a finding that was expected with the small anesthetic doses we used, and the proved hemodynamic stability of the added opioids. We found that the epidural meperidine-bupivacaine mixture caused more nausea and vomiting than fentanyl-bupivacaine mixture, this finding is very important because little data is available in this context.[15] Despite the fact that intrathecal meperidine was found to cause a high incidence of nausea and vomiting scores when compared to fentanyl and sufentanyl;[15,16] epidural meperidine compared favorably with fentanyl in the study carried out by Goh et al[8] on post cesarean section pain relief and the associated side effects including nausea and vomiting. This controversy between Goh et al result and our findings may be explained by the different type of patients they studied (post cesarean section), the different technique they used (patient controlled epidural analgesia (PCEA), or may be the smaller number of patients they enrolled in their study (45 patients versus 67 patients in our study). The secondary aim of this study was to compare the effect of meperidine and fentanyl on the fetal well-being. Our results showed that Apgar scores were <7 in only one neonate in the fentanyl group and 2 neonates in the meperidine group. The apgar scores stayed the same at 5 minutes, and the neonates had no problems then after as a result of opioid toxicity. This was in accordance with the meta-analysis performed by Reynolds et al,[17] which showed that although epidural analgesics in labor may cause some hypotension, fever, long second stage, and more instrumental vaginal deliveries; the improvement of the acid-base status and placental exchange preservation counteracts these side effects. There were no significant differences in neonatal outcome between the 2 groups although the number of neonatal admissions to the NICU in the meperidine group was more (5 neonates), compared to 2 admissions in the fentanyl group. Admission causes were obviously not related to the epidural drugs administered, but rather to other causes (mentioned earlier in the results). This suggests that both meperidine and fentanyl are safe on neonates when used in combination with local anesthetics through the epidural route.

In conclusion, despite being recently suggested that the systematically administered meperidine is ineffective in relieving labor pain, the epidurally administered meperidine is as effective as fentanyl in this context, despite being associated with more nausea and vomiting.

**Acknowledgment.** *The authors gratefully acknowledge the assistance of Hamdi Abu-Ali, MD, Raafat Daas, MD, for their help in data analysis and the translation of the Arabic Abstract.*



14Bupivacaine20061297.indd 907 5/15/07 10:17:08 AM

## References


1. Watts RW. Does pethidine still have a place in the management of labor pain? ***Aust Prescr*** 2004; 27: 34-35.
2. Olofsson C, Ekblom A, Ekman-Ordeberg G, Hjelm A, Irestedt L. Lack of analgesic effect of systemically administered morphine or pethidine on labour pain. ***Br J Obstet Gynaecol*** 1996; 103: 968-972.
3. Ngan Kee WD. Epidural pethidine: pharmacology and clinical experience. ***Anaesth Intensive Care*** 1998; 26: 247-255
4. Baraka A, Maktabi M, Noueihid R. Epidural Meperidine-Bupivacaine for Obstetric Analgesia. ***Anesth Analg*** 1982; 61: 652-656.
5. Perriss BW. Epidural Pethidine in Labour. A study of dose requirements. ***Anesthesia*** 1980; 35: 380-382.
6. Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine Release by Four Narcotics: A Double-Blind Study in Humans. ***Anesth Analg*** 1987; 66: 723-730.
7. Skjoldebrand A, Garle M, Gustafsson LL, Johansson H, Lunell NO, Rane A. Extradural pethidine with and without adrenaline during labour: wide variation in effect. ***Br J Anaesth*** 1982; 54: 415-420.
8. Goh JL, Evans SF, Pavy TJ. Patient-controlled epidural analgesia following caesarean delivery: a comparison of pethidine and fentanyl. ***Anaesth Intensive Care*** 1996; 24: 45-50.
9. Edwards ND, Hartley M, Clyburn P, Harmer M. Epidural pethidine and bupivacaine in labour. ***Anaesthesia*** 1992; 47: 435-437.
10. Fernandez-Guisasola J, Serrano ML, Cobo B, Munoz L, Plaza A, Trigo C, Del Valle SG. A Comparison of 0.0625% Bupivacaine with Fentanyl and 0.1% Ropivacaine with Fentanyl for Continuous Epidural Labor Analgesia. ***Anesth Analg*** 2001; 92: 1261-1265.
11. Debon R, Allaouchiche B, Duflo F, Boselli E, Chassard D. The Analgesic Effect of Sufentanil Combined with Ropivacaine 0.2% for Labor Analgesia: A Comparison of Three Sufentanil Doses. ***Anesth Analg*** 2001; 92: 180-183.
12. Connelly NR, Parker RK, Lucas T, El-Mansouri M, Komanduri V, Nayak P, Gutta S, et al. The Influence of a Bupivacaine and Fentanyl Epidural Infusion After Epidural Fentanyl in Patients Allowed to Ambulate in Early Labor. ***Anesth Analg*** 2001; 93: 1001-1005.
13. Chaney MA. Side effects of intrathecal and epidural opioids. ***Can J Anesth*** 1995; 42: 891-903.
14. Khaw KS, Kee WD, Critchley LA. Epidural meperidine does not cause hemodynamic changes in the term parturient. ***Can J Anesth*** 2000; 47: 155-159
15. Alain B, Ekatodramis G, Schenker C. Postoperative Nausea and Vomiting in Regional Anesthesia: A Review. ***Anesthesiology*** 2003; 98: 530-547.
16. Booth JV, Lindsay DR, Olufolabi AJ, El-Moalem HE, Penning DH, Reynolds JD. The Duke Women's Anesthesia Research Group. Subarachnoid Meperidine (Pethidine) Causes Significant Nausea and Vomiting during Labor. ***Anesthesiology*** 2000; 93: 418-421.
17. Reynolds F, Sharma SK, Seed PT. Analgesia in labour and fetal acid–base balance: a meta-analysis comparing epidural with systemic opioid analgesia. ***Br J Obstet Gynaecol*** 2002; 109: 1344-1353.




14Bupivacaine20061297.indd 908 5/15/07 10:17:09 AM