Postoperative patient-controlled epidural analgesia with opioid bupivacaine mixtures

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Purpose: To determine the efficacy and safety of patient-controlled epidural analgesia of morphine or fentanyl in combination with bupivacaine for postoperative pain relief.

Methods: Forty ASA I-II patients scheduled for major abdominal surgery were studied. After insertion of a lumbar epidural catheter, patients were given a non-opioid general anaesthetic. After surgery patients complaining of pain, received a loading dose of 2 mg morphine (Group I) or 50 µg fentanyl (Group II). For continuing pain, 1 mg morphine in 4 ml bupivacaine 0.125% (0.25 mg·ml⁻¹ morphine and 1 mg·ml⁻¹ bupivacaine, Group I) or 20 µg fentanyl in 4 ml bupivacaine 0.125% (5 µg·ml⁻¹ fentanyl and 1 mg·ml⁻¹ bupivacaine Group II) were administered. Blood pressure, heart rate, respiratory rate and SpO₂ were monitored. Assessments of pain (VAS), nausea-vomiting, motor block, pruritus and sedation were recorded for 24 hr.

Results: No difference in pain or sedation was observed between groups. The 24 hr postoperative opioid consumption was 15.50 ± 7.53 mg morphine and 555.10 ± 183.85 µg fentanyl. Total bupivacaine 0.125% consumption was 58.00 ± 30.14 ml in Group I and 101.05 ± 36.77 ml in Group II. One patient in Group II complained of motor weakness in one leg. The incidence of nausea (Group I 45%, Group II 10% $P < 0.05$) and pruritus (Group I 30%, Group II 5% $P < 0.05$) was less in patients receiving fentanyl.

Conclusion: Both methods were effective in the prevention of pain but, because of fewer side effects, fentanyl may be preferable to morphine.

Objectif : Déterminer l'efficacité et la sécurité d'emploi de l'analgésie péridurale, contrôlée par le patient, à base de morphine ou de fentanyl en combinaison avec la bupivacaine pour le soulagement de douleurs postopératoires.

Méthode : Quarante patients ASA I-II devant subir une chirurgie abdominale majeure ont été étudiés. Après l'insertion d'un cathéter péridural lombaire, les patients ont reçu un anesthésique général sans opioïde. Les patients qui ont ressenti des douleurs après l'intervention ont reçu une dose d'attaque de 2 mg de morphine (Groupe I) ou de 50 µg de fentanyl (Groupe II). Pour soulager une douleur prolongée, 1 mg de morphine dans 4 ml de bupivacaine 0,125 % (0,25 mg·ml⁻¹ de morphine et 1 mg·mg⁻¹ de bupivacaine, Groupe I) ou 20 µg de fentanyl dans 4 ml de bupivacaine 0,125 % (5 µg·ml⁻¹ de fentanyl et 1 mg·ml⁻¹ de bupivacaine, Groupe II) ont été administrés. La tension artérielle, la fréquence cardiaque, le rythme respiratoire et la SpO₂ ont été enregistrés. Les évaluations de la douleur (EVA), les nausées et les vomissements, le blocage moteur, le prurit et la sédation ont été notés pendant 24 h.

Résultats : Aucune différence n'a été observée entre les groupes concernant la douleur ou la sédation. La consommation d'opioïde pendant 24 h après l'opération a été de 15,50 ± 7,53 mg de morphine et 555,10 ± 183,85 µg de fentanyl. La consommation totale de bupivacaine 0,125 % a été de 58,00 ± 30,14 ml dans le Groupe I et de 101,05 ± 36,77 ml dans le Groupe II. Un patient du Groupe II s'est plaint de faiblesse dans une jambe. L'incidence des nausées (Groupe I : 45 %, Groupe II : 10 % ; $P < 0,05$) et de prurit (Groupe I : 30 %, Groupe II : 5 % $P < 0,05$) a été plus faible chez les patients qui ont reçu du fentanyl.

Conclusion : Les deux méthodes ont été efficaces à prévenir la douleur mais le fentanyl pourrait être plus avantageux que la morphine parce qu'il présente moins d'effets secondaires.

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THE epidural injection of morphine is an effective method for the management of postoperative pain. However the associated side effects have precluded its widespread use in a variety of clinical settings. Agents with greater lipophilicity such as fentanyl have been utilized in an attempt to avoid some of these side effects, but the short duration of action of fentanyl has been a limitation in the relief of pain.^{1,2} Patient-controlled epidural analgesia (PCEA) circumvents the problem of the short duration of bolus fentanyl and provides the opportunity to observe clinical differences between epidural fentanyl and morphine.³

Epidural administration of opioids and bupivacaine for postsurgical pain relief have resulted in better pain scores. Several authors have suggested that this combination may produce a synergistic effect, while reducing the incidence of side effects.^{4,5,6}

The present study was performed to quantitate and compare prospectively under controlled conditions, in a randomized double-blind fashion, the efficacy and safety of PCEA of morphine or fentanyl in combination with low concentrations of bupivacaine in the management of postoperative pain.

Methods

The study was approved by the Hospital Ethical Committee and informed consent was obtained from all patients. Patients were educated in the use of PCEA and the 10 cm visual analogue score (VAS) before operation. Forty ASA I-II patients scheduled for abdomino-perineal resection were included in the study. Patients with acute or chronic lung pathology, documented sleep apnoea, or in whom epidural catheter placement was contraindicated were not studied. Subjects were randomly allocated into two groups (Group I = morphine + bupivacaine, Group II = fentanyl + bupivacaine).

Patients were premedicated with 10 mg diazepam *im*, 30-45 min before surgery. Before induction of anaesthesia, a lumbar catheter was placed at the L₃₋₄ or L₄₋₅ interspace. Correct position of the catheter within the epidural space was confirmed by the establishment of neural blockade after the injection of 10 ml lidocaine 1.5%. General anaesthesia was then induced with 5-7 mg·kg⁻¹ thiopentone and 0.1 mg·kg⁻¹ vecuronium was given to facilitate tracheal intubation. Anaesthesia was maintained with halothane/nitrous oxide/oxygen. No opioid was given during the preoperative and intraoperative periods.

When the patients were sufficiently awake to follow instructions after the completion of surgery, the use of the PCA device (Abbott Pain Management Provider)

and VAS were explained again. All patients required an initial dose in the immediate postoperative period. Patients complaining of pain (baseline), received a loading dose of 2 mg morphine (Group I) or 50 µg fentanyl (Group II) in 10 ml saline. Throughout the study, in case of continuing pain, 1 mg morphine in 4 ml bupivacaine 0.125% (0.25 mg·ml⁻¹ morphine and 1 mg·ml⁻¹ bupivacaine, Group I) or 20 µg fentanyl in 4 ml of bupivacaine 0.125% (5 µg·ml⁻¹ fentanyl and 1 mg·ml⁻¹ bupivacaine, Group II) were administered. The administration parameters for the two groups were set at 15 min lockout periods and the four hour maximum dose was 32 ml (8 mg morphine + 32 mg bupivacaine for Group I and 160 µg fentanyl + 32 mg bupivacaine for Group II). If analgesia remained inadequate (pain >4 on VAS), supplements of 50 mg meperidine *im* were injected. Patients stayed on the ward during this 24 hr, and administration of other opioids or sedative agents, either systematically or epidurally, was prohibited. The PCEA was stopped after 24 hr, but the epidural catheters were left *in situ* for three days. Patients complaining of pain, received a bolus dose of 2 mg morphine epidurally in either treatment group.

The VAS scores were recorded at rest, at baseline 2, 4, 6, 12, 18 and 24 hr PCEA started. Pulse oximetry (SpO₂) was monitored for the 24 hr study period. Respiratory rate, arterial pressure, heart rate and sedation level were measured hourly. Hypotension, defined as a decrease in systolic blood pressure by 30% from baseline. Levels of sedation were measured a sedation score from 1 to 5 (1 = wide awake, 2 = eyes open, drowsy, 3 = eyes closed, rousable to verbal stimulation, 4 = eyes closed, rousable to physical stimulation, 5 = not rousable). All nausea-vomiting was recorded. For severe nausea and vomiting, 10 mg metoclopramide *iv* was administered. Pruritus was treated with 25 mg diphenhydramine *iv*. All patients had urethral catheters in place during the first postoperative day. A modified Bromage Scale was used for the assessment of motor weakness (0; No motor block, 1; Impaired hip flexion, normal knee and ankle movements, 2; Impaired hip and knee movements, normal ankle movements, 3; Impaired movements at hip, knee and ankle joints).

At the completion of the study, patients and observers recorded overall satisfaction with study drug (poor, fair, good, very good, excellent). All patients, observers (anaesthetists) and nursing staff were blinded: the syringes were prepared by one of the authors not involved with patient management.

Results were compared using Student's *t* test, Mann-Whitney U test and ² or Fisher's exact test with *P* < 0.05 was taken as significant.

Results

Complete data were obtained in 40 patients. The demographic data showed the groups were similar with respect to age, weight, sex, operation time and type of operation (Table I).

The mean VAS pain scores of patients was low in both groups during the 24 hrs of observation. There were no differences VAS between groups (Figure 1). Supplemental meperidine, was used in one patient in Group II. This patient had received a loading dose and PCEA bolus doses, but the VAS >4 at one hour after injection, and analgesia was evaluated as inadequate. There were no differences in sedation scores between the two groups at any time during the period of study.

The 24 hr postoperative opioid consumption was 15.50 ± 7.53 mg morphine and 555.10 ± 183.85 µg fentanyl. The bupivacaine 0.125% solution consumption was 58.00 ± 30.14 ml in Group I and 101.05 ± 36.77 ml in Group II.

TABLE I Demographic characteristics

	Group I (n = 20)	Group II (n = 20)
Age	50 ± 14	51 ± 12
Weight (kg)	61 ± 12	68 ± 11
Sex (M/F)	8/12	9/11
Duration of surgery (min)	243 ± 117	279 ± 133

Values given as means ± SD. No significant differences between groups

TABLE II Total opioids and bupivacaine doses used over the first 24 hr postoperatively

	Group I	Group II
Morphine (mg)	15.50 ± 7.53	—
Fentanyl (µg)	—	555.10 ± 183.85
Bupivacaine (0.125%, ml)	58.00 ± 30.14	101.05 ± 36.77

Values given as means ± SD

TABLE III The side effect profile for PCEA

	Group I (n = 20)	Group II (n = 20)
Nausea	9 (45%)	2 (10%)*
Vomiting	—	—
Pruritus	6 (30%)	1 (5%)*
Leg weakness	—	1
Numbness of trunk	—	—
Respiratory depression	—	—
Urinary retention†	—	—

* $P < 0.05$, †Urinary retention could not be evaluated due to presence of urethral catheters

There were no major or minor technical problems in any patient and in no case did respiratory depression develop. A ventilatory frequency < 10 bpm was not recorded for any patient after commencement of PCEA. In this study, desaturation did not occur in either group ($SpO_2 > 92\%$) and no patient required supplementary oxygen therapy. Heart rate and arterial pressure changes were almost identical during the study, and hypotension did not occur in the postoperative period.

The number of patients reporting nausea was lower in Group II (10%) than in Group I (45%) and no patient vomited in either group. One patient in the fentanyl group and three in the morphine group requested therapy for severe nausea. Pruritus occurred less often in Group II (5%) than in Group I (30%). Two patient in the morphine group required diphenhydramine for mild pruritus. Urinary retention could not be evaluated due to the presence of urethral catheters. One patient in Group II complained of motor weakness in one leg (grade 1) during the first postoperative day (Table III). After completion of the 24 hr study period, both the patients and the researcher rated overall satisfaction similar in both groups (Figure 2).

Discussion

Our results demonstrated that combining morphine + bupivacaine and fentanyl + bupivacaine with PCEA provides excellent postoperative analgesia. The quality of fentanyl + bupivacaine epidural analgesia did not differ from that of morphine + bupivacaine over the entire period of treatment. There have been a number of studies evaluating the efficacy and safety of epidural morphine or fentanyl in combination with bupivacaine in non-labouring patients, but these combinations have used continuous infusion epidural analgesia.^{7,8} In one

FIGURE 1 Visual analogue scores during the first 24 postoperative hours (mean ± SD).

FIGURE 2 Overall satisfaction with study drug. At the completion of the study period, both patients and observers rated overall satisfaction similar in both groups ($P > 0.05$)

study, the continuous epidural infusion of the combination of dilute local anaesthetic with fentanyl or morphine (the epidural infusion rate $5 \text{ ml} \cdot \text{hr}^{-1}$, fentanyl $10 \mu\text{g} \cdot \text{ml}^{-1}$ or morphine $0.1 \text{ mg} \cdot \text{ml}^{-1}$ both with bupivacaine 0.1%) provided high-quality analgesia with minimal side effects.⁹

There may be advantages in using PCEA routinely. Marlow *et al.* compared PCEA with a continuous epidural infusion of hydromorphone and reported that the infusion group received greater amounts of opioids than the PCEA-only group but no difference in analgesic efficacy was detected.¹⁰ Similar results were shown by Parker and co-workers who compared PCEA with PCEA + infusion using hydromorphone.¹¹ In another study the co-administration of fentanyl infusion with PCEA did not confer an increase in analgesic efficacy over 'pure' PCEA and although desaturation was more marked with PCEA + continue infusion.¹² It was suggested that psychological or pharmacological mecha-

nisms may be responsible for this difference. Reduction in anxiety may have increased the placebo effect of PCEA. Intermittent bolus administration of drugs may have allowed greater CSF penetration than with a continuous infusion. In addition, spread of epidural solution after bolus administration may be greater than with infusion. This is more likely to be a factor for opioid than for bupivacaine.

Side effects associated with bupivacaine include sympathetic blockade and resulting hypotension, as well as sensory and motor blockade yielding discomfort or difficulty with ambulation, and it is dose-dependent phenomenon.¹³ The use of epidural morphine, as with epidural bupivacaine, has been limited clinically because of the frequent occurrence of pruritus, nausea, and urinary retention, as well as the occasional occurrence of severe respiratory depression. These side effects were most noticeable when higher doses of opioid were used.⁷ Cooper *et al.*, reported that combining epidural bupivacaine and opioid decreased the requirements of each agent. Addition of bupivacaine to fentanyl led to a 24% reduction in fentanyl administration by PCEA, whilst adding fentanyl to bupivacaine led to a 21% reduction in bupivacaine administration by PCEA, and side effects were minor.¹⁴

The safety of opioid bupivacaine mixtures given by PCEA was also demonstrated in the present study. No patient suffered clinical respiratory depression. Cardiovascular stability was obtained and postoperative hypotension did not occur. A previous report, that the administration of a small volume of bupivacaine 0.125% (5 mg) with fentanyl by PCEA produced a 50% incidence of hypotension, but hypotension was seen in 40% of patients before commencement PCEA.⁴ We can only suggest that the absence of hypotension during our study may be explained by preventing hypovolaemia in the peroperative and postoperative periods. Numbness of the trunk did not appear in either group but one patient in the fentanyl group complained of slight weakness in one leg. This patient received the largest volume of solution in the study. Comparison with other studies is difficult since reports of motor symptoms are often omitted. Leg weakness is important for early mobilization. The addition of this dose of bupivacaine did not prevent early mobilisation.⁴

The incidence of nausea and pruritus was less in patients receiving fentanyl. This finding concurs with that from a previous PCEA study that found a 6% incidence of pruritus and a 4% incidence of nausea in patients receiving bupivacaine 0.125% with fentanyl $1 \mu\text{g} \cdot \text{ml}^{-1}$.¹⁵ Considerably higher doses of epidural fentanyl are sometimes used in postoperative patients but this increases the incidence of pruritus. In one study,

38% of patients receiving an epidural infusion of fentanyl at a mean dose of $1.52 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ required diphenhydramine for pruritus.¹⁶ Fisher *et al.* reported that pruritus occurred less often in the fentanyl + bupivacaine group (22%) than in the morphine + bupivacaine group (42%). In the same study it was reported the incidence of nausea was also lower in the fentanyl group (3.4%) than in the morphine group (17.4%).⁹

The higher lipophilicity of fentanyl may be responsible for the observed lower incidence of side effects. Because fentanyl is more lipophilic, it partitions itself into lipid containing structures of the spinal cord and epidural fat, thereby allowing less free fentanyl to migrate into the CSF with less rostral spread to the brain. Morphine, in contrast, is more hydrophilic and, following epidural injection, more drug is partitioned into the CSF allowing it to spread rostrally to the subependymal cells of the fourth ventricle with possible associated side effects.

The combination of dilute bupivacaine with an opioid administered into the epidural space provides good analgesia with an absence of serious side effects. However, because of the less frequent side effects, fentanyl may be preferable to morphine.

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