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Patient supplemented epidural analgesia after major abdominal surgery with bupivacaine/fentanyl or ropivacaine/fentanyl

Purpose: To compare analgesic efficacy and occurrence of motor block and other side effects during patient supplemented epidural analgesia (PSEA) with either ropivacaine/fentanyl or bupivacaine/fentanyl mixtures.

Methods: In a prospective, randomized, double-blind study, 32 ASA I-III patients undergoing major abdominal surgery received an epidural catheter at the T₈-T₁₀, followed by integrated general epidural anesthesia. Postoperative epidural analgesia was provided using a patient controlled pump with either ropivacaine 0.2%/2 µg·ml⁻¹ fentanyl (group Ropivacaine, n = 16) or bupivacaine 0.125%/2 µg·ml⁻¹ fentanyl (group Bupivacaine, n = 16) [background infusion 4 - 6 ml·hr⁻¹, 1.5 ml Incremental Doses and 20 min lock out]. Verbal pain rating score, number of incremental doses, consumption of epidural analgesic solution and rescue analgesics, sedation (four-point scale), and pulse oximetry were recorded by a blind observer for 48 hr after surgery.

Results: No differences in pain relief, motor block, degree of sedation, pulse oximetry and other side effects were observed between the two groups. The number of incremental doses and the volume of analgesic solution infused epidurally were higher in patients receiving the bupivacaine/fentanyl mixture (10 [0 - 52] I.D. and 236 [204 - 340] ml) than in patients receiving the ropivacaine/fentanyl solution (5 [0 - 50] I.D. and 208 [148 - 260] ml) ($P=0.03$ and $P=0.05$, respectively).

Conclusion: Using a ropivacaine 0.2% / 2 µg·ml⁻¹ fentanyl mixture for patient supplemented epidural analgesia after major abdominal surgery provided similar successful pain relief as bupivacaine 0.125%/2 µg·ml⁻¹ fentanyl, but patients receiving bupivacaine/fentanyl requested more supplemental.

Objectif : Comparer l'efficacité analgésique, l'occurrence de blocage moteur et autres effets secondaires pendant une analgésie épidurale complétée (AEC) avec un mélange de ropivacaine/fentanyl ou de bupivacaine/fentanyl.

Méthode : L'étude prospective, randomisée et à double insu a porté sur 32 patients d'état physique ASA I-III qui devaient subir une intervention chirurgicale abdominale majeure. Un cathéter épidural a été mis en place à T₈ - T₁₀ et une anesthésie générale/péridurale intégrée a suivi. L'analgésie épidurale postopératoire, administrée par une pompe contrôlée par le patient, comprenait soit un mélange de ropivacaine à 0,2 %/2 µg·ml⁻¹ de fentanyl (groupe Ropivacaine, n = 16) soit un mélange de bupivacaine à 0,125 %/2 µg·ml⁻¹ de fentanyl (groupe Bupivacaine, n = 16) [perfusion de base de 4-6 ml·h⁻¹, doses en incréments de 1,5 ml et période réfractaire de 20 min]. Le score verbal d'estimation de la douleur, le nombre de doses incrémentielles, la consommation d'analgésique épidural et de doses d'appoint, la sédation (selon une échelle en quatre points) et l'oxymétrie de pouls ont été enregistrés par un observateur impartial pendant 48 h après l'opération.

Résultats : Aucune différence intergroupe n'a été observée quant au soulagement de la douleur, au blocage moteur, au degré de sédation, à l'oxymétrie de pouls et aux autres effets secondaires. Le nombre de doses incrémentielles et le volume de solution analgésique administré par perfusion épidurale ont été plus élevés chez les patients du groupe Bupivacaine (10 [0 - 52] D.I. et 236 [204 - 340] ml) que chez ceux du groupe Ropivacaine (5 [0 - 50] D.I. et 208 [148 - 260] ml) ($P = 0,03$ et $P = 0,05$, respectivement).

Conclusion : Un mélange de ropivacaine à 0,2 %/2 µg·ml⁻¹ de fentanyl, comme analgésie épidurale d'appoint à la suite d'une intervention chirurgicale abdominale majeure, a fourni un soulagement de la douleur d'efficacité similaire à un mélange de bupivacaine à 0,125 %/2 µg·ml⁻¹ de fentanyl, mais ce dernier a nécessité plus de doses d'appoint.

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Accepted for publication September 12, 1999

POSTOPERATIVE epidural analgesia with local anesthetic solutions is known to have beneficial effects on patient outcome after major abdominal surgery, improving recovery of normal bowel function.¹ However, the use of local anesthetic alone for postoperative epidural analgesia is unsatisfactory because of motor blockade when administered in doses sufficient for analgesia.² Epidural opioids combined with local anesthetic solution improve the quality of postoperative analgesia reducing the dose related adverse effects of either class of drug alone.³⁻⁵

Ropivacaine is a new, long-acting local anesthetic with a more favourable toxic profile than previous long acting local anesthetics, like bupivacaine,^{6,7} and is available as a 0.2% solution for epidural analgesia. However, little information is available on the association of low concentrations of ropivacaine and fentanyl for epidural postoperative analgesia after major abdominal surgery.

We conducted a randomized, double-blinded study to compare the efficacy, motor blockade, and other side effects of patient supplemented epidural analgesia with 2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl added to either bupivacaine 0.125% or ropivacaine 0.2%.

Methods

After Hospital Ethics Committee approval and patient written informed consent had been obtained, 32 ASA physical status I-III patients, scheduled to have elective major abdominal surgery (including major bowel resection: 22, hepatic resection: 5, pancreaticoduodenectomy: 5) were randomly allocated to receive patient supplemented epidural analgesia (PSEA) with either ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Ropivacaine, $n = 16$) or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Bupivacaine, $n = 16$). Patients with contraindications to epidural catheter placement, younger than 18 yr or older than 80 yr, with allergy to local anesthetic solutions or opioids, as well as pregnant women or patients not able to understand the use of PSEA were excluded.

To calculate the required study size, we took into account the results of a pilot study with 10 patients per group (unpublished observations). We wished to detect a difference between the two analgesic mixtures in the final number of supplemental doses requested by the patient ranging between 7 and 10 doses, accepting a two-tailed α error of 5%, and a β error of 10%.⁸ Based on these calculations the required study size was 16 patients per group.

Preoperatively, patients received routine physical examination with measurement of baseline hemody-

namic parameters and pulse oximetry. At this time, patients were also instructed both on the use of patient supplemented epidural analgesia (PSEA) and the verbal rating pain scale (VRS). Before the surgical procedure, according to a computer generated table, patients were randomized in a double-blind fashion to receive ropivacaine/fentanyl or bupivacaine/fentanyl mixtures for intra- and postoperative epidural pain control. Patients were premedicated with 0.1 $\text{mg}\cdot\text{kg}^{-1}$ diazepam *po* one hour before surgery and a standard infusion of 10 $\text{ml}\cdot\text{kg}^{-1}$ Ringer's Lactate solution *iv* was given; then an epidural catheter was placed at the T₈-T₁₀ interspaces. After an epidural test dose (60 mg lidocaine 2%) confirmed the correct catheter location, epidural block up to T₄ (loss of pinprick sensation) was induced by 1 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and 8 - 10 ml of either ropivacaine 0.75% (group Ropivacaine, $n = 16$) or bupivacaine 0.5% (group Bupivacaine, $n = 16$). Intraoperative management included standardized integrated epidural - general anesthesia.⁹ General anesthesia was induced with 3 to 5 $\text{mg}\cdot\text{kg}^{-1}$ thiopental and 0.6 $\text{mg}\cdot\text{kg}^{-1}$ atracurium, and maintained with isoflurane (end tidal concentrations ranging between 0.3% and 0.5%) in a nitrous oxide 60% in oxygen mixture, with continuous atracurium infusion (0.01 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ *iv*). Epidural anesthesia was maintained with 30 - 50% of the original dose every 90 - 120 min at the discretion of the anesthesia team to maintain hemodynamic stability. Intraoperatively, no other opioids were allowed to the attending anesthesiologist. Patients were awakened and their tracheas extubated at the conclusion of surgery.

Postoperative pain relief was provided using a patient supplemented epidural analgesia (PSEA) using a standard PCA pump (CADD-PCA, Deltec, St. Paul, MN, USA). According to patient grouping, postoperative PSEA was provided with either ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl, which were prepared by one of the authors not taking further part in data collection. The PSEA infusion was initially set to deliver 4 $\text{ml}\cdot\text{hr}^{-1}$ of the study solution, with 1.5 ml incremental doses and a 20 min lock out time. If analgesia was inadequate the background infusion rate was increased to 6 $\text{ml}\cdot\text{hr}^{-1}$. If analgesia remained inadequate, and patients asked for more analgesia a non-steroidal anti-inflammatory drug was allowed as rescue analgesic (100 mg ketoprofen *iv*), while the epidural catheter was tested with 5 ml lidocaine 1% to ensure correct placement.

Non invasive arterial blood pressure, heart rate, oxygen saturation and occurrence of untoward events were measured at 1, 6, 12, 24, and 48 hr after the end of surgery. At the same time, the degree of pain, motor

blockade, and sedation were also recorded by a blind observer. Motor block was assessed using the modified Bromage scale (0 = no motor block, 1 = ankle blocked, 2 = ankle and knee blocked, 3 = ankle, knee and hip blocked). If the patient developed motor blockade higher than 1 at the modified Bromage's score, the background epidural infusion of study solution was discontinued for one hour and restarted at 4 ml·hr⁻¹. The degree of pain was measured during coughing using a Verbal Rating Scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = worst pain). Sedation was measured using a four-point sedation scale (1 = awake and alert, 2 = mildly sedated, easy to wake up when spoken to, 3 = moderately sedated, easy to wake up when slightly shaken, 4 = deeply sedated and difficult to wake up when shaken). A decrease of respiratory rate < 10 bpm together with deep sedation was considered a major respiratory complication, while reduction in oxygen saturation < 90% was treated with supplemental oxygen by face mask, and need for oxygen therapy during the postoperative period was recorded as a minor respiratory complication. At the occurrence of nausea 10 mg metoclopramide *iv* was given and the need for antiemetic drug was recorded. The total volume of analgesic solution infused and the number of incremental doses given to the patient were also recorded via interrogation of the PCA device.

Patients were seen twice a day by the surgical, anesthesia pain service, and research teams to optimize and co-ordinate care and to evaluate recovery of gastrointestinal function. The total volume of gastric damming 24 hr after surgery and the time to first passage of flatus were also recorded.

Both patients and anesthesiologist caring for postoperative analgesia and recording measured parameters were blind to the PCEA solution administered.

Statistical analysis was performed using the program Systat 7.0 (SPSS Inc, Chicago, IL). Student's *t* test was used to compare continuous variables; when data were not normally distributed the Mann-Whitney *u*-test was used. Analysis of variance for repeated measures was used to analyze changes over time. Categorical data were analyzed using the contingency table analysis with the Fisher exact test. A value of $P \leq 0.05$ was considered significant. Continuous variables are presented as mean ($\pm$ SD) or as median (range), while categorical variables are presented as number (%).

Results

No differences in the distribution of the surgical procedures was observed between the two groups. Anthropometric data of studied patients are summarized in Table I: no differences in age, weight, height,

TABLE I Anthropometric parameters of studied patients receiving PSEA with either a ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Ropivacaine, *n* = 16) or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Bupivacaine, *n* = 16) mixture.

	<i>Ropivacaine</i> (<i>n</i> = 16)	<i>Bupivacaine</i> (<i>n</i> = 16)
Age (yr)	63 $\pm$ 10	59 $\pm$ 13
Weight (kg)	67 $\pm$ 17	70 $\pm$ 12
Height (cm)	164 $\pm$ 8	165 $\pm$ 9
Sex (Male/Female)	13 / 3	9 / 7
Level of epidural catheter	T ₈ (T ₈ - T ₁₀)	T ₈ (T ₈ - T ₁₀)

Data are presented as mean $\pm$ SD, except for sex (number) and level of epidural catheter placement (median and range).

TABLE II Number of incremental doses, consumption of analgesic solution and number of rescue analgesics, degree of motor block, occurrence of untoward hemodynamic events, total volume of gastric damming 24 hr after surgery, and time to first flatus in patients receiving PSEA with either a ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Ropivacaine, *n* = 16) or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl (group Bupivacaine, *n* = 16) mixture.

	<i>Ropivacaine</i> (<i>n</i> = 16)	<i>Bupivacaine</i> (<i>n</i> = 16)	<i>P</i>
Incremental doses / 48 hr	5 (0 - 20)	10 (5 - 52)	0.03
Total PCEA volume (ml)	208 (148 - 260)	236 (204 - 340)	0.05
Number of rescue analgesics	1 (0 - 4)	2 (0 - 4)	0.21
Bromage scale for motor block (<i>n</i> of patients with scores 0/1/2/3)			
1 hr	15/1/0/0	15/0/1/0	0.69
6 hr	16/0/0/0	16/0/0/0	0.99
12 hr	16/0/0/0	14/1/1/0	0.34
24 hr	16/0/0/0	14/1/1/0	0.34
48 hr	16/0/0/0	16/0/0/0	0.99
Episodes of hypotension			
1 hr	2	1	0.99
24 hr	2	2	0.99
48 hr	1	2	0.99
Episodes of bradycardia			
1 hr	2	1	0.99
24 hr	0	1	0.99
48 hr	0	0	0.99
Residual gastric damming			
24 hr (ml)	50 (0 - 300)	50 (0 - 400)	0.97
Time to first flatus (hr)	48 (40 - 96)	48 (38 - 96)	0.78

Motor blockade and untoward hemodynamic events are presented as count; other data are presented as median (range).

and male to female ratio were observed between those patients receiving the ropivacaine/fentanyl mixture and those receiving bupivacaine/fentanyl. Table I also shows the median (range) level of epidural catheter insertion in the two studied groups.

FIGURE 1 Pain during coughing measured using a five point verbal rating score at discharge from the recovery room, and at 6, 12, 24, and 48 hr after the end of surgery in patients receiving PSEA with either a ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl (group Ropivacaine, $n = 16$) or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl (group Bupivacaine, $n = 16$) mixture.

FIGURE 2 Median (range) values of peripheral hemoglobin oxygen saturation ($\text{SpO}_2\%$) measured preoperatively and at 1, 6, 12, 24 and 48 hr after the end of surgery in patients receiving PSEA with either a ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl (group Ropivacaine, $n = 16$) or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl (group Bupivacaine, $n = 16$) mixture.

Five patients in the Ropivacaine group (31%) and seven in the Bupivacaine group (43%) required antiemetic therapy during the study period (P : NS), while one patient only in the Ropivacaine group complained of pruritus on the first postoperative day. No differences in the degree of sedation were observed between the two groups, and in no case was the level of sedation higher than grade 2 (patient mildly sedated, easy to wake up when spoken to).

There were no differences between groups in the degree of pain relief at any of the measurement times (Figure 1), and the number of rescue analgesics were similar in the two groups (Table II). However, the number of incremental doses given and the final volume of analgesic solution infused in the epidural space were

higher in patients treated with the bupivacaine/fentanyl mixture compared with those patients receiving the ropivacaine/fentanyl solution (Table II).

The incidence and severity of changes in arterial blood pressure and heart rate, as well as the degree of motor blockade was similar in the two studied groups (Table II). No differences were observed between the two groups in the residual gastric damping 24 hr after surgery and time to canalization (Table II).

No patients developed major respiratory complication requiring either oxygen therapy or naloxone administration. Oxygen saturation reduced from baseline values in both groups throughout the study period ($P < 0.05$); however, no differences were observed between the two groups (Figure 2).

Discussion

The results of this study demonstrated similarly successful pain relief when using either a ropivacaine 0.2%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl or bupivacaine 0.125%/2 $\mu\text{g}\cdot\text{mL}^{-1}$ fentanyl mixture for patient supplemented thoracic epidural analgesia after major abdominal surgery, with no differences in the incidence of motor blockade or other side effects; however, patients receiving the bupivacaine/fentanyl mixture requested more supplemental doses via the PCA machine, with a slightly increased consumption of the epidural analgesic solution. A possible explanation for this finding could be a difference in the potency ratio between ropivacaine and bupivacaine when associated with low doses of fentanyl for postoperative epidural analgesia. Various studies reported similar pattern of sensory and motor blockades with ropivacaine and bupivacaine at a dose ratio of approximately 1.5 to 1,¹⁰ suggesting that this was the equipotent dose ratio. Polley and colleagues¹¹ estimated the relative potencies of epidural ropivacaine and bupivacaine for labor analgesia by using an up-down sequential allocation study design, and demonstrated a potency ratio ranging between 1.35 to 1 and 2 to 1; while D'Angelo and colleagues¹²⁻¹⁴ reported a similar potency ratio between epidural ropivacaine and bupivacaine during labor analgesia when used with or without the addition of low doses fentanyl. According to the results of this study, the dose ratio between ropivacaine and bupivacaine allowing for similar thoracic epidural analgesia after major abdominal surgery when added to 2 $\mu\text{g}\cdot\text{mL}^{-1}$ epidural fentanyl is nearly 1.3 to 1. However, it is also important to note that the equimolar ratio at which the opioid and the local anesthetic are administered may play a role in the analgesic efficacy of a local anesthetic/opioid mixture,¹⁵ since it has been demonstrated that the enhancement of spinal opioid antinociception produced by local anesthetics is dose dependent.¹⁶

Various studies have demonstrated that the combination of epidural opioids and local anesthetics results in better pain relief than local anesthetic alone,^{5,17} allowing for the best balance of analgesia and side effects after major abdominal surgery, while accelerating postoperative recovery of gastrointestinal function and time to fulfillment of discharge criteria.¹ Our results demonstrated very good control of postoperative pain, while the effects on gastrointestinal motility and time to canalization were similar to those reported by Liu and colleagues¹ in a previous investigation. The high quality of pain relief could be also related to the combination of the pre-emptive effect of inducing the epidural blockade before skin incision^{18,19} with the synergism of multimodal analgesia.^{20,21}

Both groups showed a decrease in postoperative oxygen saturation compared with baseline values, but there were no differences between the groups. The clinical relevance of these observed decreases in oxygen saturation is questionable, because no patient required supplemental oxygen to maintain saturation > 90%. These findings agree with previous studies evaluating the respiratory effects of epidural infusion of opioid/local anesthetic mixtures in elderly patients after major joint replacement.²²

In a recent investigation comparing three different concentrations of ropivacaine and fentanyl for postoperative patient-controlled epidural analgesia, Liu and colleagues²³ demonstrated that using a ropivacaine 0.2%/4 µg·ml⁻¹ fentanyl solution allowed for a reduction in consumption of PCEA solution compared with less concentrated solutions of ropivacaine, but was associated with the development of clinically relevant motor blockade in up to 30% of patients. In the present investigation only one patient receiving the ropivacaine/fentanyl mixture developed slight motor blockade (Bromage score = 1) one hour after the end of surgery, and no differences in motor block were observed between the two groups. A possible explanation for this difference in the incidence of motor block could be the site of epidural catheter placement: contrary to the present investigation, Liu and colleagues placed the epidural catheter at low thoracic-lumbar vertebral interspaces, while placement of epidural catheters in such proximity to lumbar spinal segments providing motor innervation to the lower extremities is known to increase the risk of motor block compared with more cephalad placement.²⁴ Our observations further suggest that placing the epidural catheter at a thoracic level may help the anesthesiologist in minimizing the development of motor block during epidural analgesia after major abdominal surgery.

The positive effects on patient outcome of providing epidural analgesia after major abdominal surgery has

been clearly demonstrated^{1,25} and is widely accepted. The results of the present investigation demonstrated that patient supplemented epidural analgesia with either a ropivacaine 0.2%/2 µg·ml⁻¹ fentanyl or bupivacaine 0.125%/2 µg·ml⁻¹ fentanyl mixtures provides similarly successful pain relief after major abdominal surgery, but patients receiving the bupivacaine/fentanyl mixture requested supplemental doses more often, leading to a slight increase in consumption of analgesic solution.

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