Patient-Controlled Epidural Analgesia After Abdominal Surgery: Ropivacaine Versus Bupivacaine

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In this randomized, double-blinded study we sought to assess the analgesic efficacy of ropivacaine and bupivacaine in combination with sufentanil and the efficacy of ropivacaine alone after major abdominal surgery. Sixty patients undergoing major abdominal surgery received standardized general anesthesia combined with epidural thoracic analgesia. They were allocated to one of three groups: the BS group received postoperative patient-controlled epidural analgesia with 0.125% bupivacaine plus 0.5 μg/mL sufentanil; the RS group received 0.125% ropivacaine plus 0.5 μg/mL sufentanil; and the R group received 0.2% ropivacaine, with the patient-controlled epidural analgesia device set at bolus 2–3 mL and background infusion 3–5 mL/h. Visual analog scale scores were significantly lower during coughing in the BS group compared with the RS and R groups and in the RS group compared with the R group. The BS group required significantly less local anesthetic (milligrams per day) during the first three postoperative days compared with the RS and R groups, and the RS group, significantly less than the R group. No major side effects were noted in any group. We conclude that, after major abdominal surgery, thoracic epidural analgesia was more effective with bupivacaine than with ropivacaine when these two local anesthetics are used in a mixture with sufentanil. Ropivacaine alone was less effective than ropivacaine in combination with sufentanil.

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The aim of postoperative pain management is to relieve pain so that normal functions, including ventilation, gastrointestinal function, coughing, and mobility, are minimally impaired. For this purpose, patient-controlled epidural analgesia (PCEA) is a powerful treatment modality (1). Local anesthetics administered by the epidural route are the only drugs that suppress the stress response in patients who have undergone lower-body operations (2).

Bupivacaine is the most commonly used local anesthetic during postoperative epidural analgesia. Its use in combination with sufentanil provides better pain relief at rest and during mobilization than bupivacaine alone (3). Commercially available bupivacaine is a racemic mixture of S(−) and R(+) enantiomers. The greater toxicity of R(+) bupivacaine may be partly attributed to the increased binding of R(+) enantiomer to the sodium channels of neural or cardiac tissues (4,5). Although ropivacaine and bupivacaine are quite similar in structure, ropivacaine, a pure S(−) enantiomer, is less toxic to the cardiovascular and central nervous systems (6,7). With epidural administration in humans, the sensory- and motor-blocking effects of ropivacaine are equipotent to or less potent than those of bupivacaine (7–11). A dose-finding study in patients undergoing abdominal surgery demonstrated that 0.2% ropivacaine provided the best balance between analgesia and motor block of the lower limbs and suggested that, in contrast to bupivacaine, ropivacaine could be used without an opioid for postoperative analgesia (12). However, epidural administration of ropivacaine has never been compared with the administration of the same concentration of bupivacaine in association with a liposoluble opioid after major abdominal surgery. The aim of this study was to compare, through PCEA, the efficacy and side effects of these two local anesthetics and to assess the influence of adding sufentanil to ropivacaine after major abdominal surgery.

Methods

This prospective double-blinded study was conducted for 18 mo after approval from the Montpellier Hospital Ethical Committee. Inclusion criteria were age from
18 to 70 yr, ASA status I or II, elective major abdominal surgery for cancer via midline or bisubcostal incision, absence of contraindication to epidural anesthesia (e.g., preoperative coagulopathy or localized infection), and absence of extreme malnutrition or cerebral vascular insufficiency. The day before surgery and after written informed consent, all subjects received written and verbal instructions for use of the PCEA device. The patients were then assigned to receive, as determined by a table of random numbers, one of three epidural analgesic regimens: bupivacaine and sufentanil (BS group), ropivacaine and sufentanil (RS group), or ropivacaine alone (R group). The study drugs were prepared in identical containers.

After oral premedication with 100 mg hydroxyzine and 0.5 mg alprazolam, all patients had an epidural catheter placed at the T7–T9 level for upper abdominal surgery or the T9–T11 level for colonic surgery. Lidocaine 2% with 5 μg/mL epinephrine was injected into the epidural catheter to achieve a bilateral T4 sensory level. General anesthesia was then induced with 3–5 mg/kg thiopental and 0.2–0.4 μg/kg sufentanil, tracheal intubation was facilitated by 0.5 mg/kg atracurium, and lungs were mechanically ventilated. Anesthesia was maintained with sevoflurane (0.6–1 minimum alveolar anesthetic concentration), and muscle relaxation was maintained with additional doses of atracurium.

The BS group received a continuous infusion of bupivacaine 0.25% and a 1 μg/mL sufentanil mixture at a rate of 0 to 12 mL/h (the infusion rate was started at 3 mL/h after general anesthesia was induced and was increased if systolic arterial pressure, heart rate, or both increased to more than the initial values measured before the beginning of anesthesia; it was decreased if systolic arterial pressure decreased more than 30% less than the initial values). Postoperative epidural analgesia was provided by PCEA with a combination of 0.125% bupivacaine and 0.5 μg/mL sufentanil.

The RS group received a continuous infusion of 0.25% ropivacaine and 1 μg/mL sufentanil mixture, followed by postoperative PCEA with a combination of 0.125% ropivacaine and 0.5 μg/mL sufentanil.

The R group received a continuous infusion of 0.75% ropivacaine, followed by postoperative PCEA with 0.2% ropivacaine.

In each group, a PCEA pump (APM; Abbott Laboratories, Paris, France) was programmed to deliver a 2- or 3-mL bolus with a lockout interval of 12 min and a background infusion of 2–5 mL/h. The initial settings of the bolus and background infusion were 3 mL and 3 mL/h, respectively. Then background infusion was increased up to 5 mL/h when pain relief was inadequate (visual analog scale [VAS] score >30 mm). When systolic arterial blood pressure decreased to <90 mm Hg, background infusion and bolus were decreased to 2 mL/h and 2 mL, respectively, the patient received 500 mL hydroxyethyl starch, and, if that did not correct the hypotension, the patient received incremental 3-mg doses of ephedrine.

Tracheal extubation was performed when weaning criteria were satisfied. All patients received the same postoperative physiotherapy. The day after surgery, the patients routinely sat in an armchair with the help of the nurses. The nasogastric tube was removed when gastric suction provided <500 mL/d. From the third postoperative day, PCEA was discontinued when a dose was not necessary for at least 4 h. Before attempting to walk, patients were assessed for evidence of motor blockade or orthostatic hypotension.

To quantify the intensity of postoperative pain, the patients were asked to use a 100-mm VAS graduated from 0 (no pain) to 100 mm (the worst possible pain). VAS scores were recorded at rest and after coughing at 8:00 AM, 12:00 AM, and 8:00 PM daily. To optimize analgesia while minimizing sedation and hemodynamic instability, the patient-controlled setting could be further adjusted during the twice-daily visits of the physicians. Nurses also received extensive training regarding the study techniques. IV 2 g propacetamol or 100 mg ketoprofen was infused on request when pain relief was inadequate (VAS score >30 mm). If the epidural catheter could not be inserted or if epidural analgesia was ineffective, patients were administered self-controlled analgesia with IV morphine and were excluded from further evaluations. No other sedative, analgesic, or central nervous system-acting drug was permitted, except haloperidol and metoclopramide as necessary for postoperative delirium and nausea, respectively. An overall satisfaction score according to postoperative analgesia (nil = 0; mild = 1; good = 2; excellent = 3) was recorded on the fifth postoperative day.

Patients were assessed with a sedation scale (wide awake = 0; mildly sleepy and responsive to verbal command = 1; moderately sleepy = 2; extremely sleepy and unresponsive to nociceptive stimulation = 3). The patients were asked whether they had pruritus (yes or no) and nausea and vomiting (yes or no). These variables were recorded daily at 8:00 AM, 12:00 AM, and 8:00 PM during the first five postoperative days.

Motor function of the lower limbs was assessed daily by the patient’s ability to flex the knees and ankles. Motor blockade was evaluated in terms of a modified four-grade Bromage scale (13): 0 = no weakness; 1 = inability to raise extended leg (just able to move knee and feet); 2 = inability to flex knee (able to move feet or first digit only); 3 = inability to move any joint in legs.

Patients were assessed for return of gastrointestinal function two times a day by a physician who systematically questioned the patients and consulted nurse
observations until return of flatus, feces, and eating without nausea.

A clinical examination was performed the day before surgery and each morning of the first seven postoperative days for each patient. Clinical pulmonary complications were graded as described in a previous study (14) and were classified as a “minor” complication when they resolved spontaneously, a “moderate” complication when treatment for resolution was necessary, and a “severe” complication when significant intervention, such as mechanical ventilation or intensive care, was necessary. Chest radiographs obtained before surgery and on the first, third, and fifth postoperative days and radiographic chest abnormalities were classified into two groups: segmental atelectasis or large infiltrates, and pleural effusion. SpO2, arterial blood pressure, and heart rate were recorded every 5 min during surgery, every 20 min during early recovery, and, thereafter, every 2 h for 5 days.

On the basis of retrospective data from our institution in the same surgical population, a power analysis was performed by using postoperative pain during cough as the primary outcome variable. We calculated a sample size so that a between-group mean difference in VAS of 20 mm, with reduced pain scores in the BS group in comparison to the RS group, would permit a type I error rate of α = 0.05, and with the alternate hypothesis, the null hypothesis would be retained with a type error of β = 0.20. This analysis indicated that a sample size of 19 patients per group was necessary.

Continuous variables are presented as the mean ± sd or median (25th to 75th percentile) when data were not normally distributed, and categoric variables are presented as frequencies (percentage of patients).

Preoperative patient characteristics and intraoperative and postoperative data in the three randomized groups were compared by using the χ2 test for categoric variables. The Kruskal-Wallis test was used for continuous variables, and when statistical significance was inferred among the three groups, the comparisons were made 2 × 2 with Bonferroni’s correction.

Postoperative assessment for all variables measured over time was evaluated with Cochran-Mantel-Haenszel statistics by use of SAS (SAS Institute Inc., Cary, NC). Statistical significance was inferred for P ≤ 0.05.

**Results**

Sixty patients, who underwent scheduled major abdominal surgery at the Center Hospitalier Universitaire Montpellier over 18 mo, were randomly assigned to one of the three groups. Five patients did not complete the postoperative study and were excluded from postoperative data analysis because of absence of surgical resection (one in the R group) or technical failure with the epidural catheter (one in the BS group, one in the RS group, and two in the R group). Finally, 55 patients were considered eligible for further evaluation (19 in the BS group, 19 in the RS group, and 17 in the R group).

The three groups of patients were similar with respect to weight, age, sex, preoperative diseases, and ASA scores (Table 1). During surgery, no difference was observed in the duration and type of surgery, IV fluid requirements, and management of general anesthesia (Table 2). Patients in the R group received more local anesthetic (milligrams per hour) than those in the BS group (P = 0.0003) and the RS group (P = 0.001). There was no significant difference between the RS group and the BS group (P = 0.15). Exubation time was not different in the three groups (Table 2).

The duration of PCEA was comparable in the BS, RS, and R groups (96 [72–96] h, 96 [72–96] h, and 96 [72–120] h, respectively). Local anesthetic consumption (milligrams per day) was less in the BS than in the RS and R groups (P = 0.0003 and P = 0.0003, respectively) and was less in the RS than in the R group (P = 0.03) during the first three postoperative days (Table 3). VAS scores at rest were similar in all groups (Fig. 1). The BS group was provided significantly better pain relief than the RS and R groups, and the RS group had significantly better pain relief than the R group during the first three postoperative days (by the Cochran-Mantel-Haenszel test; P < 0.05) (Fig. 2). The satisfaction scores were not significantly different among the three groups (P = 0.07). On the first postoperative day, patients required more administration of ketoprofen in the R group than in the RS and BS groups and more in the RS group than in the BS group (P = 0.04). Patients required more administration of propacetamol in the R group than in the BS and BS groups during the first two postoperative days (P = 0.04).

Time of the first flatus (50 [26–68] h, 70 [40–74] h, and 62 [28–92] h, respectively), the first feces (64 [42–115] h, 76 [63–95] h, and 105 [76–132] h, respectively), and oral nutrition without discomfort (107 [94–141] h, 130 [99–147] h, and 120 [96–140] h, respectively) were similar in the BS, RS, and R groups. Daily oxygenation values up to the fifth postoperative day and the number of asymptomatic hypoxia episodes detected by pulse oximetry were not significantly different in the

| Table 1. Comparison of the Three Treatment Groups for Preoperative Factors |
|------------------|----------------|----------------|
|                  | BS group       | RS group       | R group       |
|                  | (n = 20)       | (n = 20)       | (n = 20)      |
| Age (yr)         | 55 ± 12        | 54 ± 11        | 57 ± 10       |
| Weight (kg)      | 69 ± 16        | 71 ± 15        | 73 ± 25       |
| Sex              | 9F/11M         | 8F/12M         | 11F/9M        |
| Patient ASA score (I/II) | 7/13 | 7/13 | 8/12 |

Values are mean ± sd or n.

BS = bupivacaine; S = sufentanil; R = ropivacaine.
Postoperative extubation time (min) 35 (15
IV ephedrine (mg) 3 (0
Incidence of systolic hypotension (<90 mm Hg) 11 (58%) 12 (63%) 15 (83%)
IV fluid requirement (L) 8 (6–13) 6 (5–8) 6 (6–8)
IV sufentanil (μg/kg) 0.4 (0.3–0.5) 0.3 (0.3–0.4) 0.3 (0.2–0.4)
Ropivacaine or bupivacaine (mg/h) 13 (11–18)* 20 (14–26)* 34 (29–38)
Surgery
Colonic
Gastrectomy 4 (21%)
Cephalic pancreatectomy 10 (52%)
Level of epidural catheter insertion T8 (T8–T9) T8 (T8–T10) T9 (T7–T10)
Duration of surgery (min) 343 – 280 ± 116 286 ± 134
Mean end-tidal sevoflurane (%) 1.1 (1–1.1) 1.2 (0.9–1.3) 1 (0.8–1.2)
Surgery
Cephalic pancreatectomy 10 (52%) 8 (42%) 7 (42%)
Gastrectomy 4 (21%) 5 (26%) 4 (22%)
Colonic 5 (26%) 6 (32%) 7 (39%)
Three groups. No patient required the administration of naloxone. Six patients in the BS group, seven in the RS group, and two in the R group presented at least one episode of SpO2 between 90% and 95%. One patient in both the RS and R groups presented at least one episode of SpO2 between 85% and 90%. The three groups had similar radiologic segmental or lobar atelectasis: five patients in the BS group, six in the RS group, and six in the R group. Two patients in the BS group, one in the RS group, and one in the R group experienced moderate pulmonary complications. Two subjects experienced atelectasis, pneumonia, and hypoventilation; one in the RS group required intubation and mechanical ventilation, and one required noninvasive ventilation in the R group.

The numbers of episodes of systolic hypotension were similar in the BS, RS, and R groups (3 [16%], 3 [16%], and 2 [12%], respectively). They were treated by simple fluid loading. Two patients presented motor blockade of the lower limbs in the R group during the first postoperative day. Time to walk bed-to-chair was similar in the BS, RS, and R groups: 38 (27–44) h, 35 (20–41) h, and 44 (24–45) h, respectively. Unassisted ambulation delay was similar in the BS, RS, and R groups (105 [60–160] h, 96 [73–111] h, and 95 [87–103] h, respectively). No patient developed infection or neurologic complications related to the epidural catheter. Four patients experienced pruritus: one in the BS and three in the RS group. The incidence of anastomosis leak (3 [16%], 2 [11%], and 3 [18%], respectively) and the length of the hospital stay (12 [9–17] days, 12 [9–17] days, and 12 [8–18] days, respectively) were similar in the BS, RS, and R groups.

**Discussion**

This study demonstrated that the addition of 0.5 μg/mL sufentanil to 0.125% ropivacaine provided

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**Table 2. Comparison of the Three Treatment Groups During Anesthesia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BS group (n = 19)</th>
<th>RS group (n = 19)</th>
<th>R group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic</td>
<td>5 (26%)</td>
<td>6 (32%)</td>
<td>7 (38%)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>4 (21%)</td>
<td>5 (26%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Cephalic pancreatectomy</td>
<td>10 (52%)</td>
<td>8 (42%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Level of epidural catheter insertion</td>
<td>T8 (T8–T9)</td>
<td>T8 (T8–T10)</td>
<td>T9 (T7–T10)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>343 ± 162</td>
<td>280 ± 116</td>
<td>286 ± 134</td>
</tr>
<tr>
<td>Mean end-tidal sevoflurane (%)</td>
<td>1.1 (1–1.1)</td>
<td>1.2 (0.9–1.3)</td>
<td>1 (0.8–1.2)</td>
</tr>
<tr>
<td>IV sufentanil (μg/kg)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.3 (0.3–0.4)</td>
<td>0.3 (0.2–0.4)</td>
</tr>
<tr>
<td>Ropivacaine or bupivacaine (mg/h)</td>
<td>13 (11–18)*</td>
<td>20 (14–26)*</td>
<td>34 (29–38)</td>
</tr>
</tbody>
</table>

**Table 3. Postoperative Patient-Controlled Analgesic Consumptions in the Three Treatment Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BS group (n = 19)</th>
<th>RS group (n = 19)</th>
<th>R group (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidual bupivacaine (mg/d)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>POD 1</td>
<td>176 (125–202)*</td>
<td>232 (191–271)*</td>
<td>348 (276–424)</td>
</tr>
<tr>
<td>POD 3</td>
<td>146 (135–176)*</td>
<td>237 (169–247)*</td>
<td>352 (270–492)</td>
</tr>
<tr>
<td>POD 4</td>
<td>140 (128–146)*</td>
<td>169 (139–188)*</td>
<td>330 (264–438)</td>
</tr>
<tr>
<td>POD 5</td>
<td>98 (79–114)</td>
<td>178 (161–196)</td>
<td>297 (246–344)</td>
</tr>
</tbody>
</table>

**Figure 1.** Postoperative pain intensity (visual analog scale [VAS]) at rest. Pain relief at rest was similar in all groups during the first three postoperative days (by the Cochran-Mantel-Haenszel test). Values are mean ± sd. B = bupivacaine; S = sufentanil; R = ropivacaine; POD = postoperative day. *P < 0.05 among the three treatment groups (Kruskal-Wallis test).
more effective postoperative epidural analgesia than 0.2% ropivacaine alone when assessing pain during coughing and that, in combination with sufentanil, ropivacaine was less effective than bupivacaine. No difference was found among the three groups for side effects related to local anesthetics or sufentanil, major morbidity, or duration of hospitalization.

Previous studies comparing ropivacaine and bupivacaine have been controversial. Sensory and motor blockade with epidural ropivacaine in women during labor has been reported to vary from equipotent with (15,16) to less potent than (17,18) bupivacaine at the same concentration. Two studies comparing these local anesthetics administered by PCEA showed that bupivacaine used at a smaller concentration than ropivacaine provided similar pain relief after major abdominal surgery (19,20). After abdominal hysterectomy, epidural analgesia with ropivacaine required more supplementary doses of ketorolac than that with bupivacaine (21). Only two clinical studies have evaluated the minimum local analgesic concentrations for epidural analgesia for women in labor (17,18). They showed that the analgesic potency of ropivacaine was 0.6 relative to bupivacaine without opioid. We observed the same result when we assessed the combination of these two local anesthetics with an opioid. The mixture of ropivacaine and sufentanil was significantly less potent than bupivacaine and sufentanil, with a consumption (milligrams per day) ratio of 0.61 to 0.75 during the first three postoperative days. Claims of reduced toxicity and motor block, when comparing ropivacaine and bupivacaine, have been made on the basis of weight comparisons in animals and volunteers. These claims have been made on the assumption of equipotency. If ropivacaine is 40% less potent than bupivacaine, the claims may no longer be valid.

The choice of the optimal concentration of local anesthetic is an important issue, determined by the best balance between pain relief and adverse effects. For bupivacaine, there is a frequent incidence of motor blockade and orthostatic hypotension at concentrations equal to or larger than 0.15% (22). Comparing 0.1%, 0.2%, and 0.3% ropivacaine, Scott et al. (12) demonstrated in patients undergoing lower abdominal surgery that 0.2% ropivacaine provided the best balance between analgesia and motor block of the lower limbs. In our study, two patients presented motor blockade of the lower limbs with 0.2% ropivacaine, but only during the first 24 hours after surgery. This could be explained by the larger concentration of ropivacaine (7.5 mg/mL) used during the surgical procedure in this group. Nevertheless, the Bromage score may not necessarily reflect the desired outcome of mobilization, as previously emphasized (20,23). No delay in ambulation or sitting in a chair was reported for the two patients who presented a transient motor blockade. Because we did not observe a delay in ambulation with 0.2% ropivacaine compared with 0.125% ropivacaine, we suggest that 0.2% ropivacaine is the optimal concentration after abdominal surgery, as previously reported (12). In contrast, Liu et al. (24) showed that a smaller concentration of ropivacaine provided less motor block, including inability to ambulate, with comparable analgesia and orthostatic hypotension incidence during PCEA for lower abdominal surgery. However, the more frequent incidence of motor blockade in their study could be explained by the insertion level of the epidural catheter at a low thoracic or lumbar level; placement of catheters in such proximity to lumbar spinal segments providing motor innervation to the lower extremities seems to increase the risk of motor block when compared with more cephalic placement (25).

Ropivacaine’s pain relief may be optimized with a liposoluble opioid addition (26,27). As reported in previous studies, we found that 0.125% ropivacaine with the addition of 0.5 μg/mL sufentanil during thoracic epidural analgesia improved the effectiveness of pain management in comparison with 0.2% ropivacaine alone after major abdominal surgery. The addition of sufentanil to ropivacaine in this study resulted in a decrease in the dose of local anesthetic required and thus would seem to be the best choice to reduce potential toxicity of local anesthetics. We observed that the addition of sufentanil did not result in a more frequent incidence of opioid-related side effects (nausea/vomiting, pruritus and hypotension, and ileus duration). However, two potential sources of bias must be pointed out: 1) there was no prospective
recovery program or discharge criteria in our institution, and 2) the power analysis of the study was performed with postoperative pain as the primary variable, meaning that we could not reach a conclusion on the incidence of side effects or rate of recovery.

In conclusion, ropivacaine was significantly less potent than bupivacaine by a factor of 0.65 when these two local anesthetics were used in combination with sufentanil to relieve pain after abdominal surgery. Epidural analgesia with a combination of ropivacaine and sufentanil was more effective than ropivacaine alone.

References