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A Comparison of 0.1% and 0.2% Ropivacaine and Bupivacaine Combined with Morphine for Postoperative Patient-Controlled Epidural Analgesia After Major Abdominal Surgery

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Ropivacaine (ROPI), which is less toxic and produces less motor block than bupivacaine (BUPI), seems attractive for epidural analgesia. Few data are available concerning dose requirements of epidural ROPI when combined with morphine. In this study, we compared the dose requirements and side effects of ROPI and BUPI combined with small-dose morphine after major abdominal surgery. Postoperatively, 60 patients were randomly allocated (double-blinded manner) to four groups: patient-controlled epidural analgesia with the same settings using 0.1% or 0.2% solution of ROPI or BUPI combined with an epidural infusion of 0.1 mg/h of morphine. Pain scores, side effects, motor block, and local anesthetic consumption were measured for 60 h. Pain scores and the incidence of side effects did not differ among the groups. Consumption of ROPI and BUPI were similar in both 0.1% groups. Doubling the concentration significantly reduced the consumption (milliliters) of BUPI ($P < 0.05$) but not of ROPI. Consequently, using ROPI 0.2% significantly increased the dose administered as compared with ROPI 0.1% (ROPI 0.1% = 314 ± 151 mg and ROPI 0.2% = 573 ± 304 mg at Hour 48; $P < 0.05$). Patient-controlled epidural analgesia with the 0.1% or 0.2% solution of ROPI or BUPI combined with epidural morphine resulted in comparable analgesia. As compared with ROPI 0.1%, the use of ROPI 0.2% increased consumption of local anesthetic without improving analgesia.

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Postoperative epidural analgesia using local anesthetic may improve patient outcome after major abdominal surgery (1,2). The more favorable toxicity profile of ropivacaine (ROPI) as compared with bupivacaine (BUPI) makes ROPI appealing for postoperative epidural analgesia (3). Although epidural ROPI produces less motor block than equal doses of BUPI (4), the doses of ROPI required when used alone to provide adequate analgesia after abdominal surgery can result in significant motor block (5). Combination with a lipophilic opioid allows reduction of the dose of ROPI, improves postoperative analgesia (6,7), and reduces the incidence of motor block (8), but is associated with undesirable opioid-induced side effects (9). Small-dose epidural morphine (0.2 mg/h) combined with BUPI provides effective epidural analgesia after abdominal surgery (10,11). However, little is known about the dose requirements of ROPI when combined with small doses of epidural morphine. Therefore, we conducted a randomized, double-blinded study to determine the doses of two different concentrations of ROPI (0.1% and 0.2%) required to produce adequate postoperative epidural analgesia after major abdominal surgery when combined with 0.1 mg/h of epidural morphine and to compare their efficacy and side effects with those of the same concentrations of BUPI.

Methods

After approval of our Institution Ethics Committee and patient informed consent, 60 ASA physical status I to III patients, scheduled for elective major abdominal surgery, were included in the study. After 6 h NPO, all patients were orally premedicated with 50 mg of hydroxyzine and 0.5 mg of alprazolam 2 h before surgery. In the operating room, an IV infusion of 10 $mL \cdot kg^{-1} \cdot h^{-1}$ of Ringer's lactate solution was started, and an epidural catheter was inserted at the

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T8-9 or T9-10 interspace. After an epidural test dose (4 mL of lidocaine 1% with 1/200,000 of epinephrine), 0.1 mL/kg of BUPI 0.5% was injected, and a continuous epidural infusion of 0.1 $mL \cdot kg^{-1} \cdot h^{-1}$ of BUPI 0.25% was started in all patients. We used BUPI in all patients to obtain the same recovery when epidural anesthesia was stopped after surgery. General anesthesia was induced with propofol (2 mg/kg), sufentanil (0.25 μg/kg), and cisatracurium (0.2 mg/kg) and maintained with sevoflurane in 50% oxygen/air mixture. Propacetamol 2 g (a precursor of paracetamol; Pro-Dafalgan®, UPSA Medica, Belgium; 2 g of propacetamol = 1 g of paracetamol or acetaminophen in the United States) was given IV 30 min before the end of surgery and then systematically every 6 h. At the end of surgery, patients were awakened, and the epidural infusion of 0.25% BUPI was stopped. Patients were then randomly allocated in a double-blinded manner to four epidural groups (n = 15 each): ROPI 0.1%, ROPI 0.2%, BUPI 0.1%, or BUPI 0.2%. The local anesthetic solution was administered using a patient-controlled epidural analgesia (PCEA) pump (Pain Management Provider; Abbott, Abbott Park, IL). PCEA settings were the same in the four groups and were a 5-mL bolus dose, lockout interval of 10 min, and no basal infusion. PCEA was combined with a continuous epidural infusion of 0.1 mg/h of morphine. Morphine was not mixed with the local anesthetic solution to keep the dose of morphine independent of the volume of local anesthetic administered. We selected a very small dose of morphine without an initial dose. Indeed, in a pilot study, the administration of a 2-mg bolus of morphine followed by a continuous infusion of 0.2 mg/h, as used by Kehlet and Mogensen (11), resulted in almost no administration of local anesthetic by the patients. Rescue analgesia was provided with IV infusion of 100 mg of tramadol every 6 h if required. The following variables were assessed 4 h after the end of surgery, and at 8:00 AM, 1:00 PM, and 6:00 PM during postoperative Days 1 and 2: (a) pain score on a 100-mm visual analog scale at rest, during coughing, and at mobilization from the supine to the sitting position, (b) motor block using the Bromage scale (1 = no motor block, 2 = knee blocked and mobility of ankle preserved, 3 = mobility of ankle difficult, and 4 = knee and ankle blocked), and (c) the level of sensory block using the cold test. Sedation score (0 = awake, 1 = drowsy, 2 = asleep, and 3 = unconscious) and respiratory rate were monitored by the nurses every 4 h. The volume of local anesthetic solution administered by the patient was recorded every 4 h. The need for rescue analgesic, nausea, vomiting, pruritus, and orthostatic hypotension (systolic blood pressure <90 mm Hg) when the patient was sitting in an armchair were also noted. Because of the systematic use of a bladder catheter, urinary retention was not reported.

Continuous variables are presented as mean ± SD, and categorical variables are represented as a number. Analysis of variance for repeated measures for two criteria (time and treatment) or the Student's t-test were used to compare continuous variables when appropriate. Categorical data were analyzed using Fisher's exact test. A value of $P < 0.05$ was considered significant.

Results

There were no significant differences among the four groups with regard to demographic and intraoperative data or type of surgery (Table 1). Pain scores at rest, during coughing, and at mobilization were comparable in the four groups (Fig. 1). Dermatomal extension of sensory block did not differ among the four groups (Fig. 2). Local anesthetic consumption in milliliters every 4 h is shown in Figure 3. There was a significant reduction of local anesthetic consumption over time in each group ($P < 0.0001$). The volumes of both 0.1% solutions administered by the patients were quite similar. With BUPI, increasing the concentration to 0.2% resulted in a significant reduction in the volume administered as compared with the 0.1% solution ($P < 0.05$). However, the volumes administered in both ROPI groups were not significantly different. Consequently, the total dose (in milligrams) of ROPI administered in the 0.2% group was significantly larger than in the 0.1% group ($P < 0.05$) (Table 2). At the postoperative Hour 48, the potency of ROPI as compared with BUPI (ratio of required dose for equivalent effect) was ≈1 (314:310) when using 0.1% solutions and ≈1.3 (573:438) when using 0.2% solutions. Those ratios remained constant between Hours 36 and 60. The need for rescue analgesics was not significantly different in the four groups (Table 3). The incidence of motor block of the legs was infrequent and not different among the groups (Table 3). Only one patient presented a high-grade (Bromage scale >2) motor block in the BUPI 0.2% group; however, no patient reported any motor block in the ROPI 0.1% group. The incidence of nausea and pruritus (Table 3) were small and not different among the groups. Four to six patients in each group presented transient orthostatic hypotension on Day 1 when they were sitting in the armchair. These hypotensive episodes all resolved after an accelerated infusion of 500 mL of Ringer's lactate solution. No decrease of the respiratory rate below 10 breaths/min was observed. Sedation scores were similar in the four groups and remained below 3 for all patients.

Discussion

This study suggests that the average dose of ROPI required to provide adequate analgesia after major abdominal surgery when given in combination with a continuous epidural infusion of morphine 0.1 mg/h is

Table 1. Patient Data

	ROPI 0.1%	ROPI 0.2%	BUPI 0.1%	BUPI 0.2%
Sex (M/F)	9/6	6/9	8/7	7/8
Age (yr)	60 ± 15	57 ± 16	61 ± 7	61 ± 14
Height (cm)	168 ± 9	164 ± 10	170 ± 8	170 ± 11
Weight (kg)	70 ± 14	67 ± 14	75 ± 13	73 ± 16
Type of surgery (gastric/hepatic/pancreatic/colic/gynecologic)	1/2/3/9/0	0/1/3/9/2	2/2/2/8/1	1/1/4/8/1
Duration of anesthesia (min)	334 ± 117	335 ± 194	347 ± 97	323 ± 114
Intraoperative sufentanil (μg)	20 ± 7	20 ± 11	20 ± 11	23 ± 9
ASA physical status (I/II/III)	3/10/2	0/13/2	3/7/5	4/9/2

Values are mean ± SD or number.
ROPI = ropivacaine; BUPI = bupivacaine.

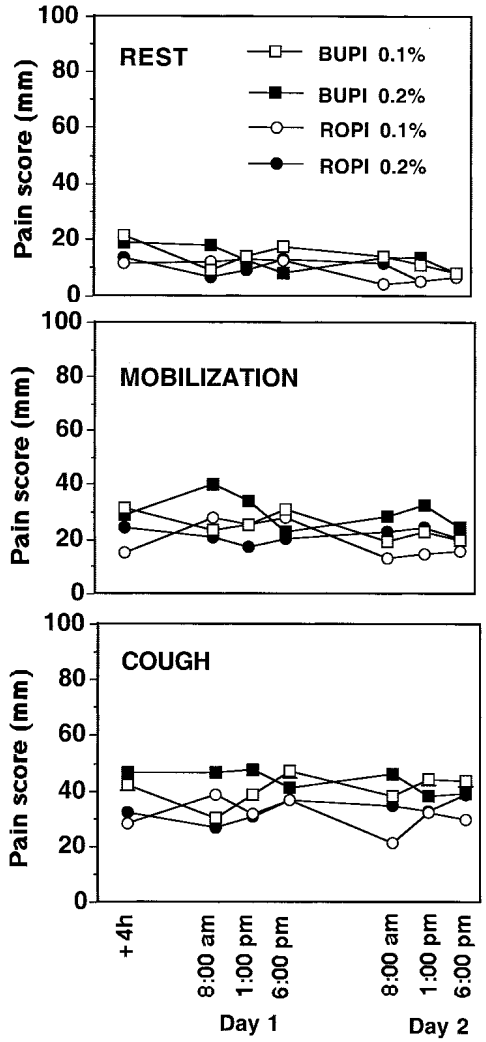

Figure 1. Pain scores at rest, during mobilization, and on coughing on a 100-mm visual analog scale. Data are mean. SEM was omitted for clarity. SEM ranged between 2 and 6 mm at rest, between 3 and 8 mm during mobilization, and between 5 and 9 mm during coughing. BUPI = bupivacaine and ROPI = ropivacaine.

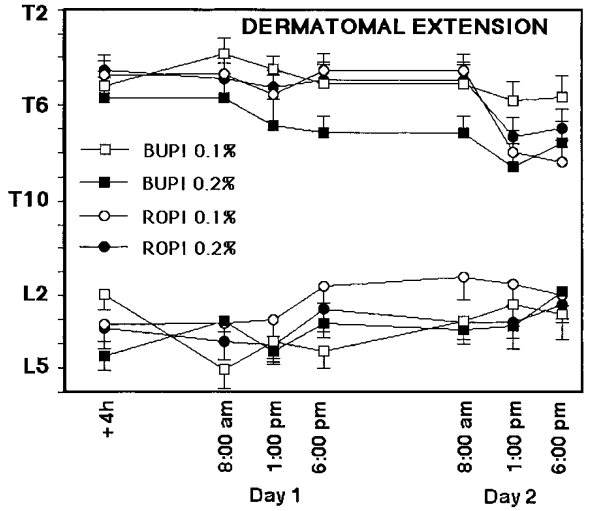

Figure 2. Dermatomal extension of anesthesia to cold. Data are mean ± SEM. BUPI = bupivacaine and ROPI = ropivacaine.

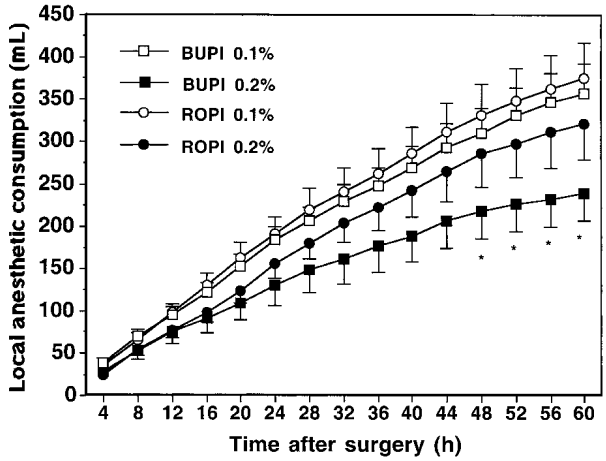

Figure 3. Local anesthetic consumption in milliliters after surgery. Data are mean ± SEM. *$P < 0.05$ as compared with ropivacaine (ROPI) 0.1% and bupivacaine (BUPI) 0.1%.

7–8 mL/h during the first postoperative 24-h period and 5–6 mL/h the next 24 h whatever the concentration of ROPI used (0.1% or 0.2%). Using PCEA combined with small-dose morphine, the efficacy and profile of side effects for 0.1% and 0.2% solutions of ROPI and BUPI were similar.

Whereas doses of epidural ROPI approximately 20–30 mg/h are required to provide good pain relief

Table 2. Local Anesthetic Consumption After Surgery

	ROPI 0.1%	BUPI 0.1%	ROPI 0.2%	BUPI 0.2%
12th h	93 ± 44 mg	95 ± 40 mg	156 ± 73 mg	152 ± 115 mg
0–12 h	(93 ± 44 mL)	(95 ± 40 mL)	(78 ± 36 mL)	(76 ± 56 mL)
24th h	181 ± 82 mg	185 ± 60 mg	312 ± 132 mg*	261 ± 182 mg
12–24 h	(88 ± 44 mL)	(90 ± 37 mL)	(78 ± 36 mL)	(55 ± 39 mL)
36th h	248 ± 120 mg	249 ± 82 mg	445 ± 205 mg*	355 ± 237 mg
24–36 h	(66 ± 47 mL)	(64 ± 30 mL)	(67 ± 42 mL)	(47 ± 37 mL)
48th h	314 ± 151 mg	310 ± 116 mg	573 ± 304 mg*	438 ± 253 mg
36–48 h	(66 ± 38 mL)	(61 ± 44 mL)	(64 ± 56 mL)	(42 ± 28 mL)
60th h	354 ± 167 mg	357 ± 139 mg	645 ± 335 mg*	480 ± 257 mg
48–60 h	(41 ± 32 mL)	(47 ± 35 mL)	(38 ± 33 mL)	(21 ± 24 mL)

Values are mean ± SD.
Total cumulated amount of local anesthetic in mg. Between parentheses is the volume administered during each 12 h period in mL/12 h.
* $P < 0.05$ as compared with ROPI 0.1%.
BUPI = bupivacaine; ROPI = ropivacaine.

Table 3. Tramadol Consumption, Incidence of Motor Block and Side Effects

	ROPI 0.1%	ROPI 0.2%	BUPI 0.1%	BUPI 0.2%
Tramadol (Day 1)	11/2/2	10/4/1	14/1/0	12/2/1
Tramadol (Day 2)	14/1/0	13/2/0	12/2/1	14/1/0
Motor block	0	1	2	1
Motor block >2	0	0	0	1
Nausea	3	2	5	2
Vomiting	0	0	1	0
Pruritus	4	1	3	1
Hypotension	6	6	6	4

Tramadol values are the number of patients requiring 0/1/2 dose(s) of 100 mg tramadol after surgery. Values are mean ± SD. The other values are number of subjects presenting the events at least once during the epidural treatment.
ROPI = ropivacaine; BUPI = bupivacaine.

when given alone (5), its combination with a lipophilic opioid, such as fentanyl (12) or sufentanil (7,13), allows the reduction of ROPI requirements to approximately 10 mg/h and decreases the incidence of motor block. Accordingly, in our study, the dose of ROPI administered by the patients in combination with a very small dose of epidural morphine ranged between 8 and 14 mg/h. Interestingly, doubling the ROPI concentration did not significantly decrease PCEA demands. As a consequence, ROPI consumption was significantly larger in the 0.2% group compared with the 0.1% group without improving quality of analgesia. A large volume of diluted solution of ROPI reduces the dose requirements of ROPI (12). Together these data suggest that small concentrations of ROPI, 0.1% or even 0.05%, are preferable, and a minimum volume of 5–10 mL/h is required (8,12).

We selected a very small dose of morphine without an initial dose. Indeed, a pilot study showed that the epidural administration of an epidural bolus injection of 2 mg of morphine followed by a continuous epidural infusion of morphine 0.2 mg/h, as used by Kehlet and Mogensen (11), resulted in almost no consumption of local anesthetic by the patients. Accordingly, Dahl et al. (10) reported no difference in pain scores at rest whether patients were treated with those small doses of epidural morphine alone or the same dose of morphine combined with a continuous infusion of BUPI 10 mg/h. We therefore administered a smaller dose of morphine that required local anesthetic to produce satisfactory analgesia to enable us to detect potential differences in dose requirements among our four groups.

The progressive reduction over time in local anesthetic consumption observed in the four groups was multifactorial. This might reflect a reduction in postoperative pain. The progressive onset of morphine analgesia might also contribute to the decreasing consumption of local anesthetic. Indeed, no initial dose of morphine was given, and the onset time of morphine epidural analgesia is slow. Although we used a very small dose of epidural morphine, that dose was effective and prevented the tachyphylaxis that is usually observed when local anesthetics are used alone (14,15). Furthermore, ROPI requirements were smaller than those reported in studies using ROPI alone (5).

Patients from each group reported similar pain scores at rest, during mobilization, and while coughing. Because a patient provided with PCEA has free access to analgesia to obtain satisfactory pain control, it is not surprising that pain scores at rest were not different in the four groups. Furthermore, the sensory block achieved with the four local anesthetic solutions was also comparable. As a consequence, pain scores

during mobilization and coughing did not differ among the groups. Recently, Pouzeratte et al. (7) also reported similar analgesia at rest with PCEA using either BUPI 0.125% or ROPI 0.125%, both combined with sufentanil 0.5 μg/mL. However, pain scores during coughing were significantly lower in the BUPI 0.125% group. We administered morphine, whereas they selected a lipophilic opioid, sufentanil. The more cephalad spread of hydrophilic opioid in the cerebrospinal fluid as compared with lipophilic opioid may be beneficial in case of upper abdominal surgery. However, we do not think that the choice of opioid can explain the discrepancy. Indeed, because they inserted the epidural catheter at the thoracic level, sufentanil exerted its analgesic effect in the metameres involved by the surgery. Moreover, others reported comparable pain scores during mobilization, coughing, and even ambulation whenever BUPI 0.125% or ROPI 0.125% were used with another lipophilic opioid, fentanyl (16). Rather, pain scores during coughing reported by patients treated with BUPI 0.125% in the Pouzeratte et al. (7) study were abnormally low (mean scores inferior to 20 mm). In a previous study by the same authors (17), patients provided with the same analgesic regimen reported pain scores during coughing between 30 and 40 mm, which are comparable with the scores of the patients in our study. Why pain scores during coughing were so low in the group treated with BUPI 0.125% is not clear.

No significant differences were observed among the four groups with regard to the incidence and the degree of motor block of the legs. The reduced consumption of ROPI in our study resulted in an infrequent incidence of motor block of the legs. Only one patient from the BUPI 0.2% group experienced a high-grade (Bromage scale >2) motor block of the legs. No motor block was detected in any patient from the ROPI 0.1% group.

Liu et al. (8) reported more frequent and more intense motor block when the same dose of ROPI was given as a 0.2% solution as compared with a 0.1% solution, although their patients used similar doses as those given in our study (60–80 mg of ROPI every 6 h). In their study, an increased incidence of motor block in the ROPI 0.2% group was clinically evidenced only when patients were tested for their ability to ambulate, which we did not assess. No significant differences were observed between the 0.1% and 0.2% solutions when they used the Bromage scale, as in our study. However, fine assessment of the intensity of motor block using surface electromyography to measure the isometric maximal force contraction of the quadriceps demonstrated significant reduction in quadriceps strength in the 0.2% group as compared with the 0.1% group (8). The location of the epidural catheter might also explain these differences. Whereas their epidural catheters were inserted at the lumbar levels, our patients had thoracic catheters. Accordingly, the use of 0.2% ROPI (~10 mg/h) for thoracic epidural analgesia in patients undergoing major abdominal surgery did not disturb early ambulation (18).

The incidence of mild orthostatic hypotension was similar to that reported in other studies (18,19). The decrease in blood pressure was transient, quickly resolved by increasing infusion of crystalloid fluid, and did not prevent the patient from sitting in his armchair. It should be remembered that our patients underwent major abdominal surgery. It is not unusual that these patients have orthostatic hypotension the day after surgery, even in the absence of epidural analgesia with local anesthetic. Because all our patients were given epidural local anesthetic, it is impossible to determine the contribution of epidural analgesia to the incidence of orthostatic hypotension.

The potency ratio between ROPI and BUPI has been the subject of many debates. When anesthetic doses and large concentrations of these local anesthetics were administered, potency ratio (ROPI/BUPI) was approximately 1.5:1 (20). When the concentrations used were small, these two local anesthetics seemed equipotent (16,20–22). Accordingly, in our study, the potency ratio between the two 0.2% solutions was 1.3, whereas this ratio was 1 between the two 0.1% solutions. It should be noted that when these small concentrations are given, the profile and the incidence of local anesthetic-induced side effects are similar whether ROPI or BUPI is used.

In conclusion, dose requirements of ROPI when combined with small doses of epidural morphine range approximately 10 mg/h. The use of a 0.1% ROPI solution allows reduction of the doses required as compared with the 0.2% solution for equivalent analgesia. Small concentrated solutions of ROPI and BUPI have similar efficacy, potency, and side effects profiles.

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