Regional Anesthesia and Pain

The addition of epidural morphine to ropivacaine improves epidural analgesia after lower abdominal surgery

[L'addition de morphine péridurale à la ropivacaïne améliore l'analgésie péridurale après une intervention chirurgicale abdominale basse]

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Purpose: To assess the analgesic and side effects of the continuous epidural infusion of 0.2% ropivacaine combined with morphine compared to both drugs alone.

Methods: In this study, both observers and patients were blinded to patient group assignment. Sixty patients scheduled to undergo lower abdominal surgery were enrolled. Patients were randomized to one of three postoperative treatment groups: 1) combination group (a combination of 0.2% ropivacaine and 0.003% morphine); 2) morphine group (0.003% morphine); or 3) ropivacaine group (0.2% ropivacaine). Postoperatively, all solutions were administered epidurally at a rate of 6 mL·hr^{-1} for 24 hr. Patients were given *iv* flurbiprofen as a supplemental analgesic on demand.

Results: The combination group showed lower visual analogue scale scores than those of patients receiving either drug alone, both at rest and on coughing. The combination group showed a slight motor block at two hours after the continuous epidural infusion, while the ropivacaine and morphine groups did not show any motor block. The incidence of itching was significantly increased in the morphine and combination groups, compared to the ropivacaine group. There was no significant difference between the numbers of patients with nausea in the three groups. No hypotension or respiratory complications were observed in the three groups.

Conclusion: The combination of epidural 0.2% ropivacaine and 0.003% morphine has more effective analgesic effects than either of the drugs alone for postoperative pain relief after lower abdominal surgery.

Objectif : *Comparer l'effet analgésique et les effets secondaires d'une perfusion péridurale continue de ropivacaïne à 0,2 % combinée à la morphine à ceux des deux médicaments employés seuls.*

Méthode : *Dans notre étude, la répartition des sujets s'est faite à l'insu des observateurs et des patients. Nous avons recruté 60 patients devant subir une intervention abdominale basse. Ils ont été répartis en trois groupes : 1) combinaison médicamenteuse (ropivacaïne à 0,2 % et morphine à 0,003 %) ; 2) morphine (morphine à 0,003 %) ; 3) ropivacaïne (ropivacaïne à 0,2 %). Après l'opération, toutes les solutions ont été administrées par voie péridurale au débit de 6 mL·h^{-1} pendant 24 h. Les patients ont reçu du flurbiprofène iv comme analgésique complémentaire sur demande.*

Résultats : *Avec la combinaison de médicaments, comparée à chacun employé seul, on a noté des scores plus bas à l'échelle visuelle analogique et ce, au repos et pendant la toux. La combinaison de médicaments a produit un léger blocage moteur deux heures après la perfusion péridurale continue, mais la ropivacaïne et la morphine n'en ont pas provoqué. L'incidence de prurit a été significativement accrue avec la morphine et la combinaison médicamenteuse, comparées à la ropivacaïne. Il n'y a pas eu de différence intergroupe significative pour l'incidence des nausées. Dans les trois groupes, aucun cas d'hypotension ou de complications respiratoires n'a été observé.*

Conclusion : *La combinaison de ropivacaïne à 0,2 % et de morphine à 0,003 % a des effets analgésiques plus efficaces que l'un ou l'autre médicament seul pour le soulagement des douleurs après une opération abdominale basse.*

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EPIDURAL analgesia is considered an effective technique for providing pain relief after abdominal surgery. Ropivacaine has less toxicity on the cardiovascular[1,2] and central nervous systems[3] and less effect on motor function than bupivacaine when used in equivalent analgesic doses.[4] However, the doses of epidural ropivacaine needed to control postoperative pain also cause hypotension and motor block.[5,6] One strategy to provide effective postoperative analgesia and to reduce unwanted side effects is the use of a combination of local anesthetics with an opioid.[7]

Fentanyl is often used with epidural local anesthetics at a concentration of 2 or 4 $\mu g \cdot mL^{-1}$ for postoperative pain management.[8] The use of fentanyl in combination with ropivacaine has been reported to improve postoperative pain at rest and on coughing without apparent motor block, compared to the effect of ropivacaine alone.[8,9] However, the combination of fentanyl and ropivacaine frequently causes hypotension, nausea, and itching.[8,9] Although epidural morphine has also been used commonly for postoperative pain management, there is little information about the analgesic effects and side effects of the combination of ropivacaine and morphine. Therefore, this study was designed to assess the analgesic and side effects of a continuous epidural infusion of 0.2% ropivacaine combined with morphine, as compared with the effects of morphine alone or of 0.2% ropivacaine alone, for pain management after lower abdominal surgery.

Materials and methods

After obtaining informed consent from each patient and approval from the Ethics Committee of our hospital, 60 patients (ASA physical status I–II) scheduled to undergo lower abdominal surgery under general anesthesia combined with epidural anesthesia were enrolled in this study. Surgical procedures were bowel resection and abdominal total hysterectomy. Exclusion criteria included age younger than 20 yr or older than 75 yr, allergy to amide local anesthetics or opioids, coexisting diseases that could affect the reliability of clinical assessments, known or suspected drug abuse, and pregnancy. In this study, both the observers and patients were blinded to patient group assignment.

All patients were premedicated with oral zopiclone (7.5 mg) 60 min before entering the operating room. In the operating room, an epidural catheter was placed at the Th10–11 or Th11–12 level, and 3 mL of 1% lidocaine with 5 $\mu g \cdot mL^{-1}$ epinephrine were administered as a test dose. If there was no evidence of *iv* or subarachnoid injection five minutes after the test dose, 1.5% lidocaine with 5 $\mu g \cdot mL^{-1}$ epinephrine were administered in an initial volume of 6 to 10 mL. The spread of sensory analgesia was assessed using the skin prick method, and a minimum sensory spread from Th6 to L1 was required bilaterally for the patient to remain in the study. General anesthesia was induced with 2 $mg \cdot kg^{-1}$ *iv* propofol. Muscle relaxation was achieved by the *iv* administration of 0.1 $mg \cdot kg^{-1}$ vecuronium bromide, and the trachea was intubated. Anesthesia was maintained with sevoflurane (1–1.5%) in air (1 $L \cdot min^{-1}$) and oxygen (1 $L \cdot min^{-1}$). Additional doses of 5 to 8 mL 1.5% lidocaine with 5 $\mu g \cdot mL^{-1}$ epinephrine were administered epidurally at the discretion of the anesthesiologist. Analgesics other than sevoflurane and epidural lidocaine were not administrated during the period of anesthetic management.

After induction of anesthesia, the patients were randomly assigned to one of three groups by using a sealed envelope technique: a combination group, which received a continuous epidural infusion of 0.2% ropivacaine combined with 0.003% morphine; a morphine alone group, which received a continuous epidural infusion of normal saline combined with 0.003% morphine; and a ropivacaine group, which received a continuous epidural infusion of 0.2% ropivacaine. When closing the peritoneum, 6 mL of each solution were administered epidurally and the continuous epidural infusion was started using a disposable pump (Coordech Syrinjector™, Daiken-iki Co., Osaka, Japan) at the rate of 6 $mL \cdot hr^{-1}$ for 24 hr. Fifty milligrams of *iv* flurbiprofen were given as a supplemental analgesic on patient demand. Non-invasive arterial blood pressure, heart rate, oxygen saturation and occurrence of untoward events were recorded at two-hour intervals postoperatively. Hypotension, defined as blood pressure below 90 mmHg, was treated with a vasopressor and/or *iv* fluid at the discretion of the investigator.

Intensity of postoperative pain was evaluated using the visual analogue scale (VAS) at rest and on coughing. The VAS consisted of a 100-mm horizontal line without gradation and with points marked as "0 mm = no pain" and "100 mm = worst possible pain." The patients were told to indicate how they felt at rest and on coughing by placing a mark perpendicular to the line. Motor blockade of the legs was evaluated using the Bromage scale (0 = no motor block; 1 = inability to flex knees 30°; 2 = inability to flex knees and ankle; 3 = complete motor block). VAS at rest and on coughing and Bromage scale were recorded at two, four, eight, 12, and 24 hr after starting the continuous epidural infusion. The occurrence of itching, nausea, and hypotension, were also noted.

On the basis of preliminary data from our institution in the same surgical population, a power analysis

TABLE I Patient characteristics

	Combination group	*Morphine group*	*Ropivacaine group*
n	19	19	20
Gender (male/female)	8/11	8/11	8/12
Age (yr)	53 ± 14	54 ± 14	52 ± 13
Height (cm)	163 ± 9	159 ± 7	160 ± 6
Weight (kg)	63 ± 12	58 ± 11	59 ± 9
Surgical procedures			
bowel resection	11	9	11
radical hysterectomy	8	10	9
Consumption of lidocaine during surgery (mL)	19	22	20

Values are expressed as mean ± SD or number. No statistical difference among the groups.

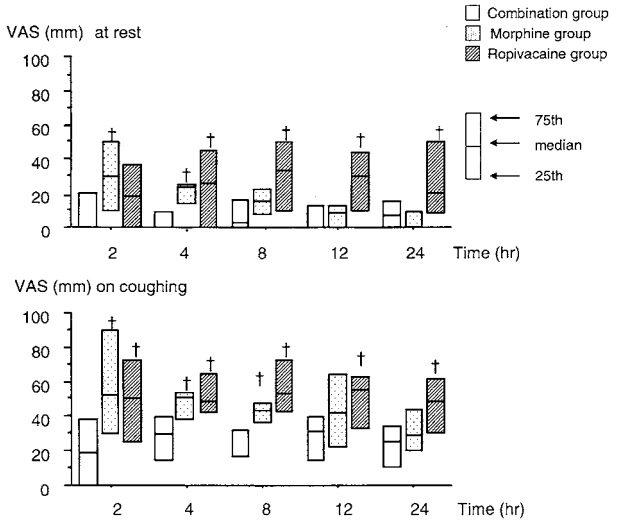

FIGURE Visual analogue scale (VAS) score at rest (upper panel) and on coughing (lower panel). Data are presented as median (25th–75th percentile). †$P < 0.05$ compared to combination group.

was performed using postoperative pain on coughing as the primary outcome variable. We calculated a sample size so that a between-group mean difference in VAS of 15 mm, with reduced pain scores in the combination group in comparison to the ropivacaine group, would permit a type 1 error rate of one-tailed $\alpha = 0.05$, and with the alternate hypothesis, the null hypothesis would be retained with a type error ß = 0.02. This analysis indicated 19 patients would be required in each group. Demographic data are presented as means ± SD. VAS data are presented as medians (25th–75th percentiles). Demographic data, the number of patients receiving supplemental analgesic, and the number of patients with nausea and itching were analyzed using the Chi-square test. VAS scores and Bromage scale were analyzed using the Kruskal-Wallis test followed by Scheffe's test. $P < 0.05$ was considered to be statistically significant.

Results

Two patients (one in the combination group and one in the morphine group) were excluded because of inadequate sensory spread. Table I shows the characteristics of the remaining 58 patients. There were no significant differences in gender ratio, age, height, weight, surgical procedures or total doses of epidural 1.5% lidocaine during surgery among the three groups.

The Figure shows the VAS scores at rest and on coughing. There were significant differences between VAS scores at rest in the combination group and the ropivacaine group at four, eight, 12 and 24 hr after starting the epidural infusion. VAS scores at rest in the morphine group were significantly higher than those in the combination group at two and four hours after starting the epidural infusion but, thereafter, the morphine group showed VAS scores comparable to the combination group. VAS scores on coughing tended to be higher compared to VAS scores at rest in all three groups. VAS scores on coughing in the combination group were significantly lower than those in the ropivacaine group throughout the observation period. The combination group also showed lower VAS scores than the morphine group at two, four and eight hours after starting the epidural infusion.

The number of patients receiving flurbiprofen was significantly lower in the combination group than in the morphine ($P = 0.01$) and ropivacaine groups ($P < 0.01$). The median number of doses of flurbiprofen

TABLE II Supplemental analgesic and incidence of side effects

	Combination group	*Morphine group*	*Ropivacaine group*
Number of patients receiving a supplemental analgesic	7/19	16/19#	20/20#
Number of doses of supplemental analgesic [median (range)]	1 (1-4)	1 (1-2)	2 (1-5)#
Number of patients with nausea	12/19	10/19	7/20
Number of patients with itching	5/19	9/19	0/20#

Values are expressed as the number of patients/total number of patients in each group. #$P < 0.05$ *vs* combination group.

TABLE III Systolic blood pressure (mmHg)

	Before anesthesia	*After epidural infusion (hr)*				
		2	*4*	*8*	*12*	*24*
Combination group	126 ± 17	110 ± 19	112 ± 11	107 ± 13	110 ± 12	112 ± 14
Morphine group	124 ± 15	112 ± 16	110 ± 17	122 ± 13	109 ± 14	116 ± 15
Ropivacaine group	122 ± 18	115 ± 17	115 ± 13	104 ± 15	113 ± 15	112 ± 15

was higher in the ropivacaine group than in the morphine ($P < 0.05$) and combination groups ($P < 0.01$; Table II).

Patients in the combination group showed a median Bromage scale of 1, two hours after initiating the epidural infusion, while patients in the ropivacaine and morphine groups showed a median Bromage scale of 0. Thereafter, median Bromage scales in all three groups were 0. The incidence of nausea was similar in the three groups (Table II). The incidence of itching was significantly increased in the morphine and combination groups compared to the ropivacaine group, so that five patients in the combination group and nine patients in the morphine group complained of itching, while no patient in the ropivacaine group complained of itching. The degree of itch was self-limited, and no medication was required. No hypotension (Table III) or respiratory complications were observed in any of the groups.

Discussion

In the present study, patients receiving a combination of epidural 0.2% ropivacaine and 0.003% morphine showed lower VAS scores both at rest and on coughing than patients receiving either drug alone after lower abdominal surgery, without causing an increase in the incidence of side effects. In addition, the number of patients receiving an additional analgesic in the combination group was smaller than in the morphine and ropivacaine groups. These data indicate that combination therapy with ropivacaine and morphine is more effective for postoperative analgesia. It should be noted that the combination of 0.2% ropivacaine with morphine was effective for pain relief during the early postoperative period, when postoperative pain is thought to be relatively intense. Epidural morphine could not suppress the postoperative pain by the four hour-time point at rest, compared to the combination of epidural ropivacaine and morphine, while the VAS score at rest in the ropivacaine group two hours after initiating the epidural infusion was not significantly different from that in the combination group. This would be due to the bolus dose given in the morphine group, which did not include ropivacaine.

The epidural infusion of 0.2% ropivacaine at the rate of 10 $mL \cdot hr^{-1}$ is thought to provide a good balance between analgesia and motor block of the lower limbs for analgesia after abdominal surgery.[5,6] However, the incidence of significant motor block 21 hr after surgery is approximately 30 to 63% in patients receiving ropivacaine at the rate of 8 to 14 $mL \cdot hr^{-1}$.[5] With the increasing emphasis on early postoperative ambulation, persistent motor blockade limits the usefulness of the epidural infusion of a local anesthetic. While the epidural infusion of 0.2% ropivacaine at the rate of 6 $mL \cdot hr^{-1}$ produces less motor block, it is less effective for postoperative analgesia than at the rate of 10 to 14 $mL \cdot hr^{-1}$.[6] Therefore, we selected the rate of 6 $mL \cdot hr^{-1}$ to reduce the incidence of motor block in our study. However, patients receiving the combination showed a weak but significant motor block two hours after the start of infusion, while patients receiving only one of the drugs did not. It has been shown that epidural morphine does not affect motor function,[10] and previous

studies showed that the addition of morphine to local anesthetics did not increase the incidence or degree of motor block.[11] We cannot explain the reason for the observed increase in the incidence of motor block in patients receiving the combination. However, the Bromage scale remained at 0 four hours after the start of the infusion until the end of the study. Therefore, the motor block observed in the combination group would not be clinically critical.

The incidence of nausea in the three groups was comparable, indicating that not only morphine but also other factors, for example patient-related factors, anxiety, type of surgery and nitrous oxide, contribute to postoperative nausea after major lower abdominal surgery.[12] The incidence of itching in the combination group and the morphine group was higher than in the ropivacaine group. We used 0.003% (0.2 $mg \cdot hr^{-1}$) morphine because this dose of morphine, combined with a low dose of bupivacaine (10 $mg \cdot hr^{-1}$), has been shown to be effective for relief of postoperative pain at rest and during mobilization from the supine position to the sitting position and also on coughing after elective major abdominal surgery.[13] A morphine concentration of less than 0.003% may significantly reduce the incidence of itching. Optimum drug combinations at minimal doses would produce powerful analgesia with lesser side effects. Further study is therefore needed to determine the optimum doses of ropivacaine and morphine in combination.

Although the addition of fentanyl to ropivacaine improves postoperative pain compared to ropivacaine alone,[8,9] the combination of fentanyl and ropivacaine frequently causes hypotension in addition to nausea and itching.[8,9] On the other hand, hypotension requiring specific treatment did not occur in any of the patients in the present study. Therefore, the combination of epidural morphine and ropivacaine may be more desirable than the combination of epidural fentanyl and ropivacaine.

In conclusion, the combination of epidural 0.2% ropivacaine and 0.003% morphine is more effective than either drug alone for postoperative pain relief after lower abdominal surgery without causing an increase in the incidence of nausea or hypotension, although the incidence of itching in the combination group was higher than that in the ropivacaine alone group.

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