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Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with i.v. PCA morphine

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Summary

We have compared the quality of three regimens of postoperative analgesia (continuous epidural administration of ropivacaine (Ropi. group), epidural ropivacaine and patient-controlled analgesia (PCA) with i.v. morphine (Ropi.+PCA group) and PCA morphine alone (PCA group)) during the first postoperative 24 h in a multicentre, randomized, prospective study. Postoperative analgesia was studied in 130 patients after major abdominal surgery performed under general anaesthesia. The ropivacaine groups received 20 ml of epidural bolus ropivacaine 2 mg ml^{-1} via the epidural route at the end of surgery, followed by continuous infusion of 10 ml h^{-1} for 24 h. The Ropi.+PCA group also had access to i.v. PCA morphine 1 mg, with a 5-min lockout. The PCA group received morphine as the sole postoperative pain treatment. The two ropivacaine groups had lower pain scores ($P<0.01$) than the PCA group. Morphine consumption was higher in the PCA group ($P<0.05$) than in the two ropivacaine groups. The quality of pain relief was rated as good or excellent in 79–85% of patients in the three groups. The percentage of patients without motor block increased between 4 and 24 h from 61% to 89% in the Ropi. group, and from 51% to 71% in the Ropi.+PCA group. (*Br. J. Anaesth.* 1998; **81**: 887–892).

Keywords: analgesic techniques, epidural; analgesia, patient-controlled; anaesthetic local, ropivacaine; pain, postoperative; surgery, abdominal

Continuous epidural infusion of a low concentration of local anaesthetic, alone or in combination with opioids, provides sustained profound analgesia with minimal sedation after major surgical procedures.[1,2] For example, postoperative epidural infusion of bupivacaine is more effective than parenteral opioids, especially during mobilization, and may reduce either postoperative morbidity or length of hospital stay.[3–7] However, toxic effects have been reported for epidural bupivacaine caused by excessive doses, low individual toxic thresholds or unrecognized intravascular injections.[8–10] Therefore, it is important that the analgesia regimens do not expose patients to an increased risk of toxic or less serious adverse effects.[4,11]

A safer substitute may be ropivacaine. Ropivacaine is a new, long-acting local anaesthetic chemically homologous to bupivacaine and mepivacaine.[12,13] In addition, ropivacaine is in the form of the S-enantiomer, making it the first enantiomerically pure local anaesthetic. Preclinical studies showed that ropivacaine induced less central nervous system and cardiac toxicity than bupivacaine.[14–18] The same decreased toxicity has been reported for ropivacaine given i.v. in human volunteers.[19,20] Further, ropivacaine induces less motor block than bupivacaine.[13,14,21] However, as yet few studies have evaluated the efficacy and safety of epidural ropivacaine (0.2%) on a large homogenous population after major abdominal surgery.[13]

Therefore, we have conducted a multicentre, open, randomized study comparing three postoperative analgesia regimens: continuous epidural ropivacaine (Ropi. group), patient-controlled analgesia with i.v. morphine (PCA group) and a combination of epidural ropivacaine and PCA morphine (Ropi.+PCA group) during the first 24 h after major abdominal surgery.

Patients and methods

After obtaining written informed consent and Institutional Ethics Committee approval, we studied 141 patients from seven hospitals. Inclusion criteria were: patients undergoing cystectomy, radical abdominal hysterectomy with pelvic lymphadenectomy, colon resection or rectum amputation, aged 18–75 yr, ASA I–III and weight 50–110 kg. Patients were excluded if they had contraindications to epidural analgesia or concomitant disease which would influence postoperative assessments.

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Patients were premedicated with lorazepam. Randomization code envelopes were opened by the investigator immediately before preparation for anaesthesia. After the randomization code was broken, the patient number was written on all labels pertaining to the study drug. Surgery was performed before 12:00 under general anaesthesia (thiopental (thiopentone), fentanyl, neuromuscular blocking drugs, isoflurane, and nitrous oxide in oxygen). After surgery, patients were allocated to one of the following three groups according to the randomization. Ropi. group: 20-ml bolus dose of ropivacaine 2 mg ml^{-1} (40 mg) followed by continuous infusion of 2 mg ml^{-1} at a rate of 10 ml h^{-1} (20 mg h^{-1}). The infusion rate was then reduced when excessive block occurred; PCA group: 1 mg i.v. bolus doses of morphine via a PCA device with a 5-min lockout time and no background infusion; Ropi.+PCA group: epidural ropivacaine as in the Ropi. group plus PCA morphine as in the PCA group.

The epidural catheter in the ropivacaine groups was inserted 4–5 cm (aimed cephalad) before induction of general anaesthesia using a 16–18-gauge needle at the appropriate interspace. A 3-ml test dose of 2% lidocaine (lignocaine) with epinephrine (adrenaline) was injected before surgery. In the PCA groups, a PCA device was connected (Abbott LifeCare PCA Infuser, Abbott Laboratories, North Chicago, IL, USA) and set to deliver 1-mg bolus doses of morphine with a 5-min lockout time. Morphine titration in the recovery room was via the PCA device after surgery. The amount of morphine used and number of demands were recorded. Additional 1–2 mg i.v. bolus doses of morphine were administered on request in all three groups.

Would pain was assessed at rest and on coughing using a 100-mm visual analogue scale (VAS, 0 mm = no pain; 100 mm = worst pain imaginable) every hour from the end of surgery to 22:00 and thereafter every 2 h if the patient was awake. Spread of sensory block was determined by pinprick for loss and return of sensation, and motor block was assessed according to a modified Bromage scale (0 = no motor block; 1 = inability to raise extended legs; 2 = inability to flex knees; 3 = inability to flex ankle joints). Block assessment was performed every 2 h (except between 22:00 and 08:00) until return of normal sensation and motor function. Patients rated the quality of pain relief (excellent, good, intermediate or poor) at 22:00 on the day of surgery, at 08:00 on the following morning and 24 h after surgery. Arterial pressure, heart rate and body temperature were recorded every 2 h after surgery.

Adverse events were recorded as follows: spontaneously reported by the patient; observed by the research team or the ward personnel; and reported by the patient in response to open and active questions. Haemoglobin arterial saturation (Sp_{O_2}) less than 90% at any time during the study for 1 min was recorded as an adverse event. Hypotension and hypertension were defined as those episodes requiring specific treatment.

Statistical analysis was performed using SAS software (version 6.08; SAS Institute, Cary, NC, USA). Patient characteristics and intraoperative data were compared using Student's *t* test for continuous variables (normal distribution) and chi-square analysis for category variables. All postoperative variables (except adverse events) were compared with the stratum adjusted Wilcoxon (mid) rank sum test adjusted for centre. The Wilcoxon test was accompanied by Bonferroni's correction. No statistical analysis was performed on adverse events. Differences were considered statistically significant at $P \leq 0.05$. Results are expressed as mean (SD) or median (interquartile or range).

Results

Of the 141 patients enrolled, 130 patients were valid for analysis of efficacy data. Treatment for pain was discontinued in four patients because of adverse events: one patient (Ropi. group) had respiratory depression after 1.3 h and was reintubated; one patient (Ropi. group) had surgical complications after 2.5 h of infusion; and in two patients (Ropi.+PCA group and PCA group), haemorrhage occurred requiring further surgery. Seven patients were excluded from analysis because they did not receive any of the study drug: two patients withdrew their consent before surgery (Ropi. group and Ropi.+PCA group), three patients had technical failures with the epidural catheter (one in the Ropi. group and two in the Ropi.+PCA group), one patient had dural puncture (Ropi. group) and one patient underwent another surgical procedure (PCA group). The three groups were similar in age, height, weight and ASA status, but there were more women in the PCA group. Duration of surgery was similar between groups (table 1). The amounts of fentanyl (approximately 500 μg), blood loss (approximately 600 ml) and i.v. fluid requirements (approximately 4000 ml) during surgery were similar in the three groups.

Times to commencement of epidural infusion–connection of PCA device were similar in all groups. The dose of epidural ropivacaine was similar in the ropivacaine groups. Median total morphine consumption was 3.5 mg in the Ropi. group, 19.0 mg in the Ropi.+PCA group ($P<0.05$) and 51.2 mg in the PCA group ($P<0.05$ compared with the Ropi.+PCA group; $P<0.01$ compared with the Ropi. group). The median number of PCA demands was 21 for the Ropi.+PCA group whereas the corresponding value for the PCA group was 78 (table 2).

Pain scores at rest and during coughing were lower in the two ropivacaine groups compared with the PCA group, a finding that was more pronounced during the early part of the postoperative period (figs 1, 2). Pain scores in the ropivacaine groups were similar throughout. Median pain scores at rest over the 24-h postoperative period were 7–20 mm in the Ropi. group, 0–14 mm in the Ropi.+PCA group, and 13–

Table 1 Patient characteristics and duration of surgery (mean (SD))

	Group		
	Ropi. ($n=38$)	Ropi.+PCA ($n=46$)	PCA ($n=46$)
Age (yr)	57 (12)	59 (12)	56 (13)
Height (cm)	166 (9)	166 (8)	169 (8)
Weight (kg)	71 (12)	68 (14)	71 (12)
Sex (M/F)	15/23	19/27	30/16
ASA I/II/III	20/18/0	22/21/3	23/22/1
Duration of surgery (h)	3.7 (1.3)	3.7 (1.2)	3.6 (1.4)

Table 2 Details of postoperative analgesia over 24 h in the three groups: Ropi. group = epidural ropivacaine, Ropi + PCA group = epidural ropivacaine and i.v. PCA morphine, PCA group = i.v. PCA morphine only. Values are median (range). *$P<0.05$ compared with Ropi. group **$P<0.05$ compared with the Ropi. + PCA group. For PCA attempts, only 44 patients in each group were recorded

	Group		
	Ropi ($n=38$)	Ropi. + PCA ($n=46$)	PCA ($n=46$)
Epidural analgesia			
Epidural catheter insertion level	T12–L1	L1–L2	
Time from end of surgery to start of epidural infusion (min)	30 (6–104)	30 (0–72)	
Epidural ropivacaine (mg)	510 (411–531)	508 (397–522)	
I.v. analgesia			
Time from end of surgery to connection to PCA (min)		84 (24–360)	84 (18–300)
Total PCA morphine (mg)		19 (0–112)	41 (7–109)
PCA attempts (n)		21 (0–801)	78 (8–520)**
PCA accepted/demands		0.75 (0.14–1)	0.61 (0.12–1)**
Total i.v. morphine (mg)	4 (0–46)	19 (0–114)*	51 (8–131)**

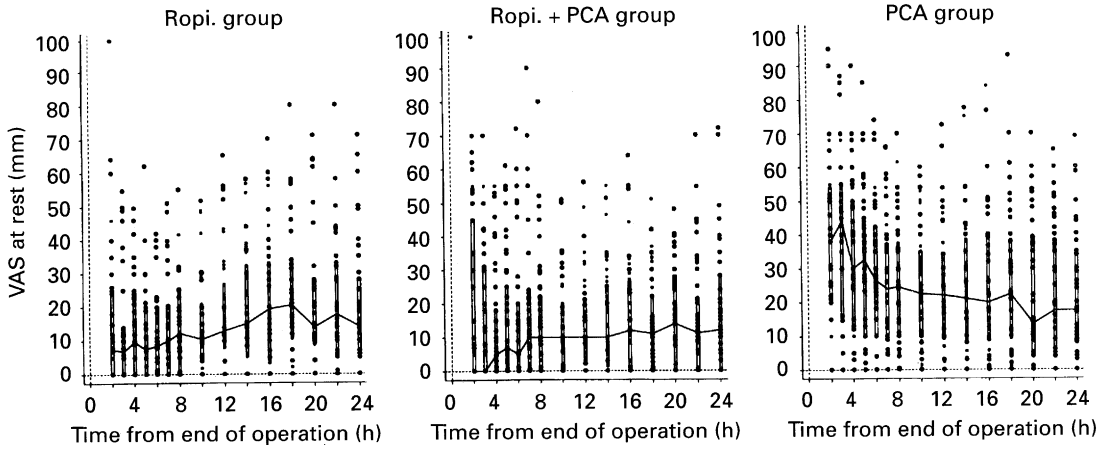

Figure 1 Pain scores at rest (VAS, 0–100 mm) during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) ($n=38$), ropivacaine and PCA morphine (Ropi. + PCA) ($n=45$–46) or PCA morphine (PCA) ($n=46$) (individual values and box plots (25th and 75th percentiles); median scores are joined).

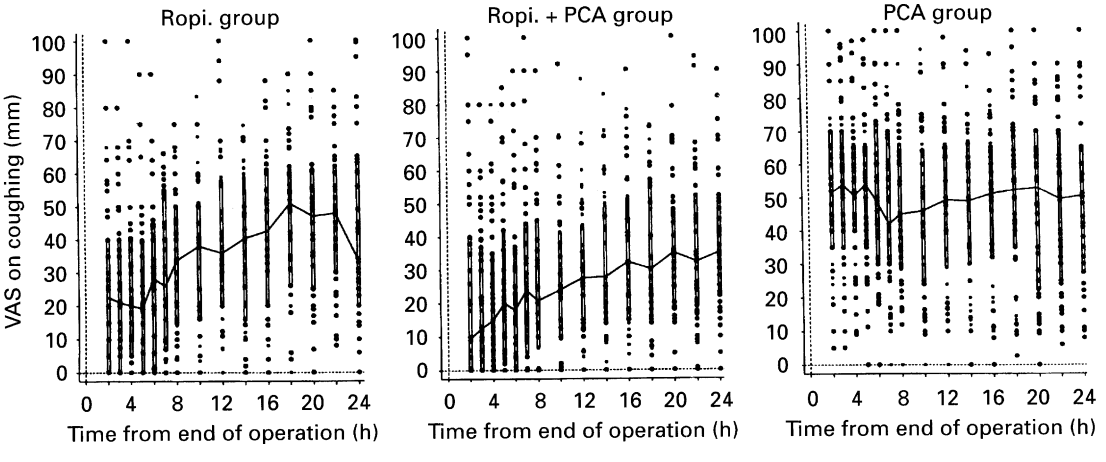

Figure 2 Pain scores during coughing (VAS, 0–100 mm) during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) ($n=38$), ropivacaine and PCA morphine (Ropi. + PCA) ($n=45$–46) or PCA morphine (PCA) ($n=46$) (individual values and box plots (25th and 75th percentiles); median scores are joined).

44 mm in the PCA group. Median pain scores during coughing varied over time and were 19–51 mm in the Ropi. group, 9–35 mm in the Ropi. + PCA group and 42–54 mm in the PCA group. Comparison of the area under the curve divided by time (AUC) for VAS during coughing and at rest over 0–24 h showed a statistically significant lower AUC value for the two ropivacaine groups ($P<0.02$). There was no significant difference in AUC between the two ropivacaine groups.

The quality of pain relief assessed at 22:00 on the day of surgery was rated as good or excellent in 84% and 87% of patients in the Ropi. and Ropi. + PCA

groups, respectively, compared with 64% in the PCA group ($P<0.05$). There were no significant difference between the groups at subsequent assessments.

Upper and lower spread of sensory block was similar in the two ropivacaine groups. Slight regression of the upper distribution was seen over time and was more pronounced in the Ropi. group ($P<0.05$) (fig. 3).

Motor block was less intense in patients who received ropivacaine alone than in those who received ropivacaine with PCA morphine. Sixty-one percent of patients in the Ropi. group and 51% in the Ropi. + PCA group had no demonstrable motor block 4 h after surgery. At 24 h the corresponding values were 89% and 71% (fig. 4).

The most common adverse events during the 24-h postoperative period are shown in table 3. Nausea and peripheral oxygen desaturation (<90%) were similar in all groups. Hypotension occurred more often in the Ropi. + PCA group, whereas hypertension was more common in the PCA group.

Discussion

We have demonstrated that epidural ropivacaine 2 mg ml^{-1} with or without PCA morphine provided more effective analgesia than PCA morphine alone, after major abdominal surgery. Addition of i.v. PCA morphine to epidural ropivacaine did not improve pain relief. Moreover, epidural ropivacaine reduced morphine consumption significantly compared with PCA alone. All treatment modalities were well tolerated.

With regard to pain relief, our results were comparable with other studies, and confirm that the quality of pain relief is superior with epidural analgesia using local anaesthetic compared with parenteral analgesia with opioids.[22] The combination of epidural local anaesthetics and opioids may improve pain relief and maintain sensory analgesia compared with epidural local anaesthetic alone.[22 23] Few studies have shown that local anaesthetic alone is capable of providing efficient prolonged postoperative analgesia without causing serious adverse effects.[22] However, no syner-

Table 3 Summary of the most common adverse events during the 24-h postoperative period (number of patients). No statistical analysis was performed

	Group		
	Ropi. ($n=38$)	Ropi.+PCA ($n=46$)	PCA ($n=46$)
Nausea	16	17	13
$Sp_{O_2} \leq 90\%$	13	11	13
Hypotension	9	18	2
Vomiting	11	8	6
Hypertension	2	4	11

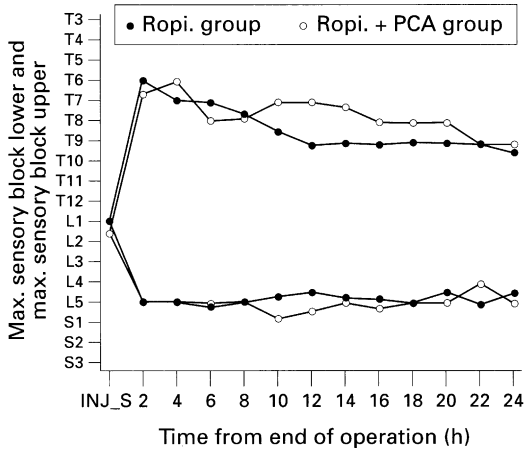

Figure 3 Upper and lower spread of sensory block during the 24-h postoperative period in patients treated with ropivacaine (Ropi.) ($n=38$) or ropivacaine and PCA morphine (Ropi. + PCA) ($n=45$–46) (median).

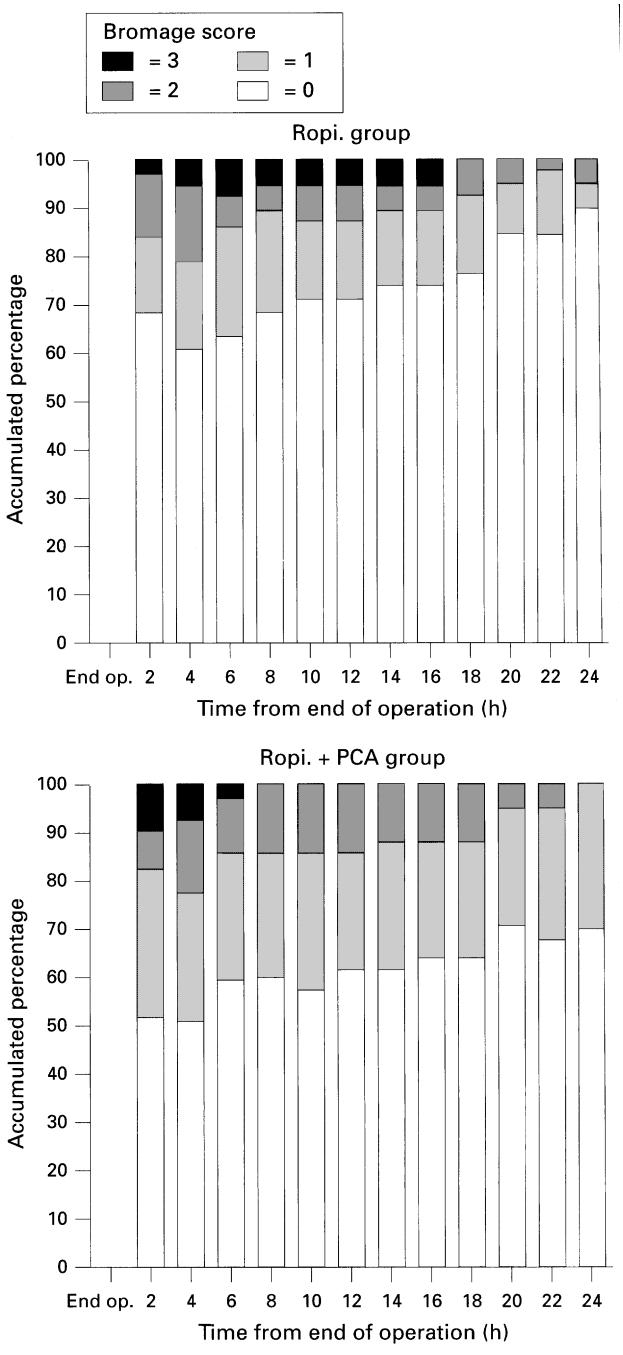

Figure 4 Motor block during the 24-h postoperative period. Modified Bromage Scale (0 = no motor block; 1 = inability to raise extended legs; 2 = inability to flex knees; 3 = inability to flex ankle joints). Cumulated frequency of patients in the ropivacaine group (Ropi.) ($n=38$) or ropivacaine and PCA morphine group (Ropi. + PCA) ($n=45$–46).

gistic effect for pain relief was demonstrated when i.v. morphine was added to epidural ropivacaine in our study, except for regression of the sensory level of analgesia. In a previous study, co-administration of epidural bupivacaine with i.v. morphine restored the sensory level of analgesia and, unlike that observed in our study, enhanced the quality of analgesia.[24]

Analgesia was not optimal in every patient in the ropivacaine groups. Suboptimal pain relief in some patients may be explained by inadequate doses of the analgesic, inadequate level of sensory block or catheter misplacement. Interestingly, patients in the Ropi. + PCA group who had easy access to supplementary morphine, consumed more opioid than those in the Ropi. group, suggesting that pain tolerance depends on environment, but the higher morphine consumption in the Ropi. + PCA group could jeopardize the rate of recovery.[3 7] However, PCA attempts were significantly less frequent in the Ropi. + PCA group than in the PCA group. Also, the delivery/demand ratio for the PCA device was higher in the Ropi. + PCA group than in the PCA group. The successful PCA attempts or the high PCA accepted/demands ratio were probably attributable to better quality of pain relief observed in the Ropi. + PCA group during the first night. It has been shown previously that the ratio between successful delivery of morphine and requests is correlated inversely with the degree of pain reported by VAS.[25] The optimal combination of local anaesthetics and opioids providing optimal analgesia and minimal complications has yet to be identified. Moreover, the use of only local anaesthetic could help to avoid opioid-induced side effects and in this study, addition of i.v. morphine did not improve pain relief. Several studies have investigated the use of continuous epidural infusions of ropivacaine as pain relief after either upper, lower or orthopaedic surgery.[26–31] Pain (either at rest or induced by coughing) becomes proportionally less severe as the dose of ropivacaine increases. Also, morphine consumption decreases as the dose of ropivacaine increases.[26–31] Scott and colleagues concluded that for postoperative analgesia, an epidural infusion of 0.2% ropivacaine provided the best balance of analgesia with minimal motor block.[27] In our study, we only evaluated the effect of a single dose of epidural ropivacaine (0.2%) on a large homogenous population after major abdominal surgery (mean duration 3.6 ± 1.3 h).

Motor block, which is undesirable in a postoperative situation, becomes more intense as the dose of ropivacaine increases.[27 28 30 31] However, in a study using different concentrations (1, 2 and 3 mg ml^{-1}) of mid-low thoracic epidural ropivacaine after upper abdominal surgery, motor block was negligible (10% of patients with Bromage scores of 1 and 2).[26] In our study, a higher incidence of motor block was observed with regression over time. The incidence of significant motor block was similar to that of a previous study conducted under the same conditions.[28] A possible explanation for the higher intensity of motor block in the combined treatment group could be a synergistic effect on the central nervous system of ropivacaine combined with PCA morphine.[32] Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of ropivacaine and bupivacaine produce a similar pattern of sensory block but motor block is slower in onset, less intense and shorter in duration with ropivacaine.[14 21 23] Large myelinated A fibres transmit motor impulses. The rate of block of A fibres depends on the physicochemical properties of the drugs, high pKa and low lipid solubility favouring block of C fibres over A fibres.[34] Ropivacaine is less likely to block A fibres than bupivacaine. This has been confirmed *in vitro*.[35]

The most frequently reported adverse event during the 24-h postoperative period was nausea, which occurred with a similar frequency in the three groups. Vomiting was slightly more common in patients treated with ropivacaine alone than in patients given PCA morphine. These events may have occurred because all patients received fentanyl during general anaesthesia and because the surgical procedure itself may also have contributed to the onset of these side effects. Hypotension was seen more frequently in patients given ropivacaine. The incidence of systemic hypotension in our Ropi. group (22%) was similar to that of our previous study and to that of others.[5 14 22] In contrast, hypertension was observed more often in patients receiving PCA morphine alone.

In summary, epidural ropivacaine administered as a continuous infusion of 2 mg ml^{-1} with or without i.v. PCA morphine gave superior postoperative pain relief both at rest and on coughing in patients undergoing major abdominal surgery than PCA morphine alone. The benefit/risk ratio of potent postoperative analgesia treatment has to be evaluated constantly.

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