Patient-controlled epidural analgesia reduces analgesic requirements compared to continuous epidural infusion after major abdominal surgery

[L'analgésie péridurale auto-contrôlée, comparée à une perfusion péridurale continue, réduit les besoins analgésiques après une intervention chirurgicale majeure]

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Purpose: To compare the quality of pain relief and incidence of side effects between 24-hr postoperative continuous epidural infusion (CEI) and subsequent patient-controlled epidural analgesia (PCEA) with different analgesics after major abdominal surgery.

Methods: Twenty-eight women undergoing extended gynecological tumour surgery received postoperative CEI with 0.15 mL·kg^{-1}·hr^{-1} 0.2% ropivacaine (R: $n = 14$) or 0.125% bupivacaine plus 0.5 μg·mL^{-1} sufentanil (BS: $n = 14$) during 24 postoperative hours. Twenty-four hours later, postoperative pain management was switched to PCEA without background infusion and 5 mL single bolus application of R or BS every 20 min at most. Visual analogue scales (VAS; 1–100 mm) were assessed by patients at rest and on coughing after 24 hr of CEI and PCEA. Side effects, doses of local anesthetics and opioids were recorded and plasma concentrations of total and unbound ropivacaine and bupivacaine were measured.

Results: Patients required lower doses of each respective analgesic medication with PCEA (R: 108 ± 30 mL; BS: 110 ± 28 mL) than with CEI (R: 234 ± 40; BS: 260 ± 45; $P < 0.01$). Ropivacaine plasma concentrations were lower 24 hr after PCEA when compared with CEI ($P < 0.01$). No patient after PCEA but two after CEI ($n = 4$; NS) presented motor block. PCEA with R provided better postoperative pain relief than CEI (37 ± 32 *vs* 59±27, $P < 0.05$). No difference in parenteral opioid rescue medication between CEI and PCEA was seen.

Conclusion: PCEA in comparison to preceding CEI provides equivalent analgesia with lower local anesthetic doses and plasma levels, and without motor blocking side effects, irrespective of the applied drug regimen.

Objectif : *Comparer la qualité de l'analgésie et l'incidence d'effets secondaires entre une perfusion postopératoire péridurale continue (PPC) de 24 h et une analgésie péridurale auto-contrôlée (APAC) ultérieure, réalisée avec différents analgésiques après une intervention chirurgicale majeure.*

Méthode : *Vingt-huit femmes, devant subir l'ablation élargie d'une tumeur gynécologique, ont reçu une PPC postopératoire avec 0,15 mL·kg^{-1}·hr^{-1} de ropivacaïne à 0,2 % (R : $n = 14$) ou de bupivacaïne à 0,125 % plus 0,5 μg·mL^{-1} de sufentanil (BS : $n = 14$) pendant 24 h après l'opération. La PPC a été ensuite remplacée par une APAC, sans perfusion d'appoint, et avec l'application d'un unique bolus de 5 mL de R ou de BS toutes les 20 min au plus. L'échelle visuelle analogique (EVA ; 1–100 mm) a été évaluée par les patientes au repos et pendant la toux après 24 h de PPC et d'APAC. Les effets secondaires, les doses d'anesthésiques locaux et d'opioïdes ont été notées et les concentrations plasmatiques de ropivacaïne et de bupivacaïne totales et libres, mesurées.*

Résultats : *Les patientes ont demandé de plus faibles doses de chacun des analgésiques avec l'APAC (R : 108 ± 30 mL ; BS: 110 ± 28 mL) qu'avec la PPC (R : 234 ± 40 ; BS: 260 ± 45 ; $P < 0,01$). Les concentrations plasmatiques de ropivacaïne étaient plus faibles 24 h après l'APAC, comparée à la PPC ($P < 0,01$). Aucune patiente n'a présenté de bloc moteur après l'administration d'APAC, mais deux après la PPC ($n = 4$; NS). L'APAC avec R s'est révélée meilleure que la PPC comme analgésique postopératoire (37 ± 32 vs 59 ± 27, $P < 0,05$). Nous n'avons observé aucune différence de médication de secours, avec opioïde parentéral, entre la PPC et l'APAC.*

Conclusion : *L'APAC, comparée à la PPC qui a précédé, fournit une analgésie équivalente pour des doses d'anesthésique local et des niveaux plasmatiques plus faibles et sans les effets secondaires de bloc moteur, peu importe le régime médicamenteux appliqué.*

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STUDIES have shown that postoperative analgesia using epidural catheters offers the opportunity to provide excellent pain relief devoid of the side effects that are associated with the parenteral application of potent analgesics.[1,2] However, continuous epidural infusion (CEI) of highly concentrated local anesthetics (LA) can cause increasing motor weakness and includes the risk of systemic toxicity. There are several means to reduce these drawbacks, e.g., insertion of epidural catheters at the center of the involved segments and the use of low concentrations of LA plus opioids.[3–6]

Patient-controlled epidural analgesia (PCEA) may offer the opportunity to reduce the incidence of side effects associated with CEI,[7] since PCEA provides excellent postoperative analgesia with only minimal side effects when properly used.[8] Both improved analgesia with similar doses of analgesics[7] and dose-sparing effects with comparable analgesia[9] have been shown for PCEA when compared with CEI.

The present prospective randomized double-blinded study examined the hypothesis that PCEA without background infusion provides comparable pain relief with lower doses of different analgesics when compared with a preceding 24 hr CEI using the same analgesics in women undergoing major abdominal surgery.

Methods

After approval of the local Ethics Committee and informed written consent, 30 women undergoing major gynecological tumour surgery were included in the study. In all patients, ovarian cancer was assumed based on the clinical investigation. Exclusion criteria were preoperative pain score > 10 on visual analogue scale (VAS; 0–100), consumption of analgesics including aspirin, coagulopathy, mental disorders, known allergic reactions to LA and severe anatomical abnormalities of the vertebral column. Patients were scheduled for median longitudinal laparotomy, hysterectomy and resection of the ovaries and exploration of the entire abdomen with resection of all tumour-infiltrated tissues (debulking). Since ovarian cancer is characterized by the production of ascites and *ip* metastases, resection of the greater omentum, liver segments or parts of the diaphragm was performed in case of a positive intraoperative histology.

A thoracic epidural catheter (22-G polyamide endhole catheter, B. Braun, Germany) was inserted at T 8 ± 2 on the morning of the operation. Aspiration and injection of a 3-mL test dose with 2% mepivacaine excluded accidental intravascular or subarachnoid catheter position. General anesthesia was then induced with sufentanil (0.4 $\mu g \cdot kg^{-1}$), etomidate (0.25 $mg \cdot kg^{-1}$) and cisatracurium (0.15 $mg \cdot kg^{-1}$) and maintained with 0.6–1.0 vol% isoflurane and nitrous oxide (FiO_2 = 0.3). Sufentanil boluses (10 µg) were repeated if patients suffered from inadequate analgesia. Six to 10 mL of the respective LA (depending on the patients' age: patients aged between 40 and 50 yr received 10 mL; between 50 and 60 yr 8 mL; and between 60 and 70 yr 6 mL) were injected in the epidural catheter at least 30 min prior to start of the operation, followed by a dose of 5 mL every 90 min. Patients were randomly allocated to receive ropivacaine 0.75% (AstraZeneca, Germany) in group R, or bupivacaine 0.5% (AstraZeneca, Germany) in group BS. Figure 1 shows a schematic flow-sheet of the protocol.

After completion of surgery, the epidural catheters were connected to an infusion pump (Perfusor, B. Braun, Germany) and the patients were transferred to the intensive care unit (ICU) before they were extubated. According to the randomization protocol, patients received 6–10 $mL \cdot hr^{-1}$ (depending on age, as described above) 0.2% ropivacaine in group R or 0.125% bupivacaine plus 0.5 $\mu g \cdot mL^{-1}$ sufentanil in group BS. The epidural infusion was maintained for the first 24 postoperative hours. Epidural top-up doses of 5 mL of the

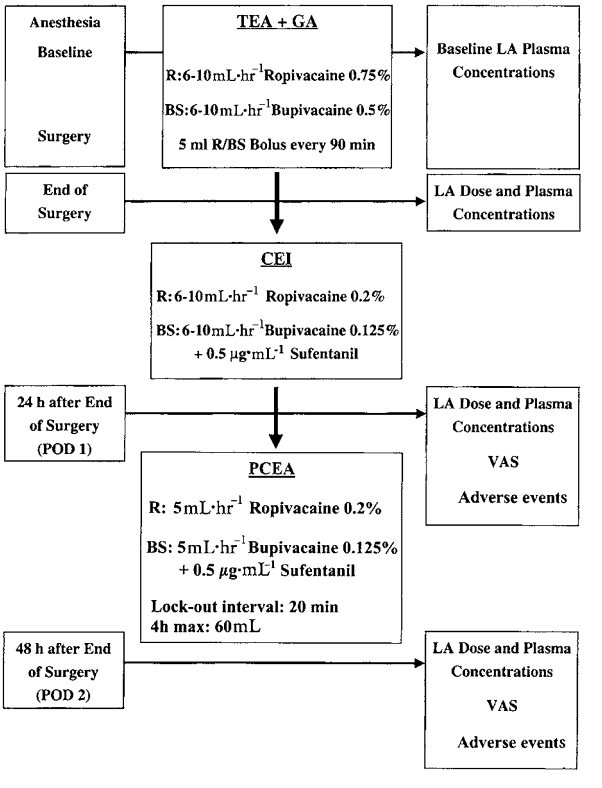

FIGURE 1 Overview of the study protocol.

TABLE I Demographic and perioperative characteristics

	Ropivacaine (R) (n =14)	*Bupivacaine/ Sufentanil (BS)* (n = 14)	*P*
Age (yr)	62 ± 17	51 ± 12	0.06
Height (cm)	164 ± 5	166 ± 9	0.47
Weight (kg)	61.2 ± 11.0	68.9 ± 17.8	0.18
ASA class I/II/III	3/9/2	3/10/1	0.64
Duration of operation (min)	245 ± 137	217 ± 135	0.29
Epidural local anesthetic intraoperatively (mL)	14 ± 4	15 ± 6	0.61
iv sufentanil intraoperatively (μg)	54 ± 28	58 ± 52	0.80
Duration of postoperative mechanical ventilation in intensive care unit (min)	240 ± 310	197 ± 248	0.45

Data presented as mean ± SD.

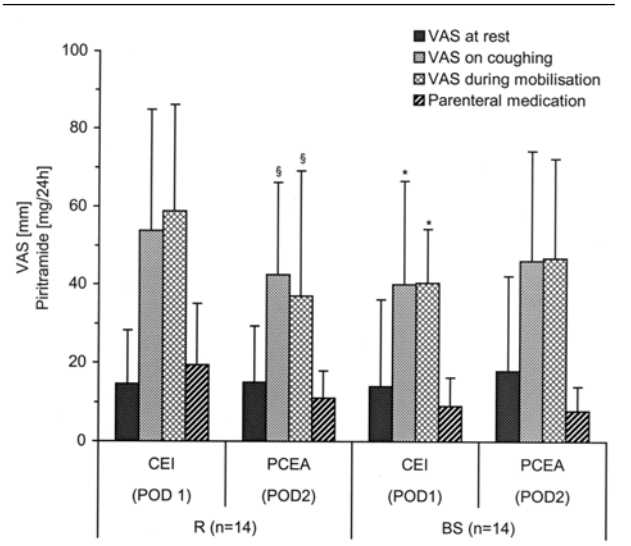

FIGURE 2 Visual analogue scale (VAS) pain scores (0–100 mm) at rest, on coughing and during mobilization after 24 hr of continuous epidural administration (CEI: POD 1) and after 24 hr of patient-controlled epidural administration (PCEA: POD 2) using only ropivacaine (R) or a mixture of bupivacaine/sufentanil (BS). The dose of the parenteral opioid medication is represented by the very right column. Data presented as mean ± SD. *P < 0.05 R *vs* BS; §P < 0.05 CEI (POD 1) *vs* PCEA (POD 2).

respective solution were administered if patients reached a VAS of ≥ 50 mm. If the top-up did not result in a pain reduction of ≥ 20 mm an *iv* bolus injection of 3.75 mg piritramide was given (Janssen-Cilag, Germany; 15 mg piritramide are equivalent to 10 mg morphine).[10] The analgesic technique was changed to PCEA 24 hr after the start of the CEI. The epidural catheter was connected to a patient-controlled analgesia (PCA) device (Graseby 9500, SIMS, Germany). All patients were allowed to inject themselves 5 mL of the respective analgesic (0.2% ropivacaine or 0.125% bupivacaine plus 0.5 $\mu g \cdot mL^{-1}$ sufentanil) every 20 min with a four-hour maximum dose of 60 mL, irrespective of their age. No background infusion was administered. Rescue pain medication with 3.75 mg piritramide *iv* was administered on demand.

After 24 hr of epidural infusion (= 24 hr after the end of surgery on POD 1) and after 24 hr of PCEA (POD 2), patients were examined by an investigator blinded to the study group. The quality of analgesia was assessed using a VAS (range from 0 mm = no pain to 100 mm = unbearable pain) by the patients at rest, during forced breathing or coughing and during mobilization out of bed. Motor function was assessed using the Bromage scale (0 = none, full flexion of both legs against gravity; 1 = partial, patient is able to move feet and knees but is not able to elevate his legs against gravity; 2 = almost complete, patient is able to move feet but not knees; 3 = complete, patient is unable to move feet or knees). Side effects such as nausea, emesis, respiratory depression (< 8 $breaths \cdot min^{-1}$) and pruritus were recorded every eight hours. The dose of epidural analgesic and of parenteral opioid was recorded at the end of the operation, after 24 hr of CEI and after 24 hr of PCEA. Before the first epidural injection (baseline), at completion of surgery, after 24 hr of CEI and after 24 hr of PCEA, central venous blood samples were taken for measurements of the plasma concentrations of the respective LA. All samples were centrifuged immediately, and the supernatant serum was frozen at -30°C until the day of measurement. Using high-pressure liquid chromatography, the total concentration and free (unbound) fraction of ropivacaine and bupivacaine were measured as described previously.[11] The accuracy of this assay is 95% and the confidence interval is ± 1.25%.

Sample size calculation and statistical analysis

For sample size calculation of the main goal of the study (CEI *vs* PCEA), a power analysis was performed by using the cumulative consumption of administered study solution over 24 hr as the primary outcome variable on the basis of retrospective data from our institution in the same surgical population. We set 9 $mL \cdot hr^{-1}$ as the mean dose of epidurally required analgesics, i.e., a cumulative dose of 216 mL over the first 24 hr. For calculation of the sample size we defined the smallest clinically significant difference between POD 1 and

TABLE II 24 hr doses of ropivacaine (R) and bupivacaine/sufentanil (BS) and plasma concentrations of the respective local anesthetic after 24 hr CEI (POD 1) and 24 hr PCEA (POD 2).

	R (n = 14)			*BS (n = 14)*		
	End of surgery	*CEI (POD 1)*	*PCEA (POD 2)*	*End of surgery*	*CEI (POD 1)*	*PCEA (POD 2)*
Total 24hr volume (mL) including volume of top-ups	Ø	234 ± 40 (top-up: 89 ± 20)	108 ± 30§	Ø	260 ± 45 (top-up: 61 ± 18)	110 ± 28§
24 hr LA dose (mg)	Ø	468 ± 80	216 ± 60§	Ø	(B) 325 ± 56* (S) 0.13 ± 0.028	(B) 137 ± 44§ (S) 0.055 ± 0.022§
Total LA plasma concentration ($ng \cdot mL^{-1}$)	625 ± 306	1905 ± 1075$	890 ± 968§	275 ± 168	572 ± 244$	405 ± 327
Free (unbound) LA plasma concentration ($ng \cdot mL^{-1}$)	41.3 ± 21.5	68.6 ± 43.3$	15.3 ± 17.0$§	1.1 ± 2.0	2.4 ± 4.1	0 ± 2.9

Data presented as mean ± SD. $\$P < 0.05$ *vs* End of surgery, $\S P < 0.05$ CEI (POD 1) *vs* PCEA (POD 2), $*P < 0.05$ BS *vs* R. CEI = continuous epidural infusion; PCEA = patient-controlled epidural analgesia; LA = local anesthetic.

POD 2 as 25% (54 mL) of the cumulative amount of epidural analgesics over the first 24 hr. The anticipated pooled standard deviation was set at 40 mL. We would permit a type I error of $\alpha = 0.05$, and with the alternate hypothesis, the null hypothesis would be retained with a type II error of ß = 0.1. This analysis reaches a power of 0.9 and indicated that a sample size of at least 13 patients per group was necessary.

In addition, patients were allocated to one of the two groups of analgesic regimen by a computerized randomization program (second goal of the study). A power analysis revealed that under the unexpected assumption of significant differences between the two analgesic regimens (VAS difference ≥ 30 mm), a sample size of 14 patients would be sufficient.

Data are reported as mean values ± SD if not stated otherwise. Differences within groups were tested by ANOVA for repeated measurements and post-hoc comparison by paired Student's t test. Differences between groups were tested by the unpaired Student's t test. Nonparametric data were tested by the Chi-square test. All differences were considered significant at $P < 0.05$.

Results

In one patient of both the R and BS groups the epidural catheter was withdrawn on the morning of POD 1 because sufficient analgesia could not be achieved. These patients were excluded from the study. The completed data of the remaining 28 patients could be evaluated. The demographic and perioperative data are shown in Table I. No significant differences were seen between groups R and BS. A median laparotomy was performed in all patients. In 87% of cases, the ovaries, uterus, parailiac and para-aortic lymphatic nodes were resected. Further resection of the greater omentum, parts of the peritoneum, parts of the intestine, bowel or bladder was performed in 50% of patients. A resection of parts of the liver, diaphragm or the spleen due to positive intraoperative histology was required in five cases (three in group BS and two in group R). In two patients (one per group) an undiagnosed pancreatic carcinoma required a partial duodeno-pancreatectomy. The intensity of surgical treatment, duration of operation and of postoperative mechanical ventilation were comparable between groups.

All patients obtained sufficient pain reduction by their thoracic epidural catheters plus parenteral medication. At rest, VAS pain scores were below 20 (Figure 2). No differences between CEI and PCEA or between the different analgesic regimens could be detected. On coughing and during mobilization out of bed, patients of group BS showed lower pain scores than patients of group R on POD 1. Patients in the ropivacaine group had higher pain scores during CEI when compared with the following 24 hr using PCEA. The doses of the parenteral opioid required were not different between groups or between POD 1 (CEI) or POD 2 (PCEA).

During CEI (POD 1), patients in group R received 234 ± 40 mL 24 hr^{-1} ropivacaine 0.2% resulting in a mean dose of 468 mg ropivacaine (Table II). While the mean infusion rate in group BS (260 ± 45 $mL \cdot 24\ hr^{-1}$) did not differ from group R, the lower concentration resulted in a lower 24 hr dose of bupivacaine (325 mg). On POD 2, PCEA doses were significantly lower when compared to CEI on POD 1, irrespective of the epidural solution. Total plasma concentrations of ropivacaine post CEI (POD 1) were significantly higher on POD 1

TABLE III Incidence of adverse events after CEI and PCEA with ropivacaine 0.2% (R) or bupivacaine 0.125% plus 0.5 μg·mL^{-1} sufentanil (BS).

	R (n = 14)		*BS (n =14)*	
	CEI (POD 1)	*PCEA (POD 2)*	*CEI (POD 1)*	*PCEA (POD 2)*
Motor function of lower extremity				
Bromage (0/1/2/3)	11/3/0/0	14/0/0/0	12/2/0/0	14/0/0/0
Nausea	3	4	5	2
Vomiting	3	2	5	1
Pruritus	0	1	3	4
Respiratory depression	0	0	0	0

No significant differences between groups and between CEI and PCEA. CEI = continuous epidural infusion; PCEA = patient-controlled epidural analgesia.

when compared with PCEA on POD 2 (Table II). In group BS, the decrease of the plasma concentrations of bupivacaine between POD 1 and 2 was not significant.

During CEI, five patients (three of group R and two of group BS) showed impaired motor function of their lower extremities (Bromage grade 1). No patient suffered from any motor restriction on POD 2 after 24 hr of PCEA (Table III). Hemodynamic variables were comparable between groups over time. The incidence of nausea, vomiting or pruritus did not differ between POD 1 and 2, nor between group R and BS. No patient had signs of respiratory depression. Due to indwelling catheters, the bladder function could not be evaluated in our patients. No adverse events, associated with epidural analgesia, such as postdural puncture headache or neurological deficits, were observed within a postoperative period of seven days.

Discussion

Our study was designed to compare the efficacy of PCEA *vs* thoracic CEI with different analgesic drug regimens after major abdominal tumour surgery. This protocol was chosen because postoperative mechanical ventilation in the ICU was mandatory for several hours after such extensive operations. During this period, patients would not have been able to use a PCEA. Our data show that PCEA provides at least as good or even better (R group) postoperative pain relief as CEI with comparable side effects irrespective of the applied drugs. We were able to demonstrate a reduction of the epidurally applied study solution using PCEA compared with CEI. Comparable results have already been shown by Silvasti *et al.* in two different groups of patients with CEA or PCEA after spinal anesthesia for knee arthroplasty.[12] Our results may be limited by the fact that the same patients, who served as their own controls, received CEI on POD 1 and PCEA on POD 2. Theoretically, the decrease in epidural requirements may result from excellent or even excessive epidural analgesia on POD 1. However, top-up injections and additional parenteral opioid application during POD 1 were required, making this effect unlikely. In addition, there is no evidence for a reduction of postoperative pain during the first 48 hr after major surgery in the literature. Although hardly comparable, a nearly constant need for medication to reach adequate pain relief during the first three to four postoperative days has been reported.[4,13,14] Wiebalck *et al.*[4] investigated a group of patients undergoing a variety of operations including abdominal, vascular and thoracic surgery. Patients appear to require a higher dose of epidurally administered drugs for comparable pain relief on the second postoperative day compared to POD 1, possibly because of forced mobilization on POD 2. In patients after gastrectomy, Komatsu *et al.*[13] showed a nearly constant need for analgesics administered via PCEA during the first 48 postoperative hours. Brodner *et al.*[14] observed that, after major gastrointestinal surgery, dynamic pain was maximal on the first and second postoperative days and decreased three days after surgery. In addition, it would have been difficult to randomize a comparable group of patients to CEI or PCEA, since the sensitivity to pain is highly divergent and variable among patients. However, the impact of the preceding pain management on the efficacy of PCEA remains somewhat unclear.

There is a (randomization-related) trend to a higher mean age in group R when compared with group BS, although the difference was not statistically significant ($P = 0.06$) per study protocol, younger patients received a larger volume of LA solution. However, the higher age was not associated with a lower intraoperative mean dose of LA in group R *vs* BS (14 *vs* 15 mL), but was associated with a lower LA volume on POD 1 after 24 hr with CEI (R: 234 mL *vs* BS: 260 mL). The similar intraoperative dose of LA can be explained by the slightly longer duration of operation in group R which led to a higher percentage of reinjections during the case and may have counteracted the age difference. More importantly, the youngest women (45 and 48 yr) were included in group R leading to a higher LA dose of 10 mL in these patients. In addition, a higher cumulative top-up dose was required in the R group (89 ± 20 mL) when compared with the BS group (61 ± 18 mL) during CEI making the expected difference between R and BS on POD 1 smaller. This difference in required top-ups

may probably be explained by the lower potency of R in comparison with BS. In a follow-up study we could show that 0.375% ropivacaine is equivalent to BS in patients undergoing major abdominal surgery.[15] In this study we were investigating the opioid-free epidural administration of an LA solution, because epidural opioids can cause major problems in patients with sleep apnea syndrome or result in side effects like respiratory depression and sedation caused by the vascular uptake of the opioid. In identical concentrations, ropivacaine appears to be less potent than bupivacaine.[16] Therefore we used a higher concentration of ropivacaine. Ropivacaine appears to have an advantage over other long acting LA because of a pronounced differential blocking effect[17] and a lower severity of cardiac side effects in case of systemic intoxication.[18]

Irrespective of the applied drug regimen, comparable or even better pain relief could be obtained during PCEA with significantly lower doses of the respective analgesic than with CEI. This is reflected by the lower plasma concentrations of ropivacaine during PCEA when compared with CEI. In contrast, no significant decrease of the bupivacaine plasma concentrations could be detected, possibly due to the smaller amount of dose reduction during PCEA *vs* CEI and a longer plasma-half-life of bupivacaine in comparison to ropivacaine.[19] Even when the higher concentration and doses of epidural ropivacaine are considered, the absolute plasma concentrations of ropivacaine were relatively higher than the plasma concentrations of bupivacaine. This result is consistent with other studies, which measured higher plasma concentrations of ropivacaine *vs* bupivacaine after equivalent epidural doses.[20] However, all plasma concentrations of ropivacaine and bupivacaine, especially the unbound fraction, measured in this study were far below the threshold at which severe central nervous and cardiac side effects have been reported.[21] The reduction of LA plasma concentrations may be an advantage of PCEA over CEI in terms of safety.

In contrast to CEI, no signs of motor block were observed with PCEA. Although an earlier study did not demonstrate a decrease in the incidence of motor block by using PCEA,[9] a reduced rate of motor block may reflect an advantage of PCEA over CEI in postoperative pain management.

In accordance with other studies[3–5] our results suggest that supplementation of a low concentration of LA with an opioid provides better pain relief than a LA used as the sole agent during the early postoperative period when patients are mobilized.

Increasing evidence suggests that epidural anesthesia and analgesia provide better outcomes after major surgical interventions[2,8,22,23] and that epidural analgesia using thoracic catheters is more and more frequent.[24] Although both CEI and PCEA have been shown to be safe and effective for the management of postoperative pain,[25,26] we prefer to use PCEA whenever patients are able to use the device. This may help avoid unnecessarily high LA plasma concentrations and motor blockade. In addition, the unique advantage of PCEA over continuous infusion is the patient's ability to obtain analgesia at the appropriate time, e.g., before physical exercise and mobilization. Only a few conditions may limit the use of PCA – whether epidural or *iv* – such as postoperative mechanical ventilation in highly sedated patients. Extremes of age should not be an exclusion criteria for PCEA, since the successful use of PCEA has been documented in elderly patients[27] as well as in children.[28] Further studies will be required to demonstrate whether the pain scores obtained with PCEA during stress and mobilization in our study can be improved by using low-dose background infusions[13,29] or a low dose/high volume concept.[30]

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