Influence of central neuraxial blockade on anesthetic pharmacology and brain function

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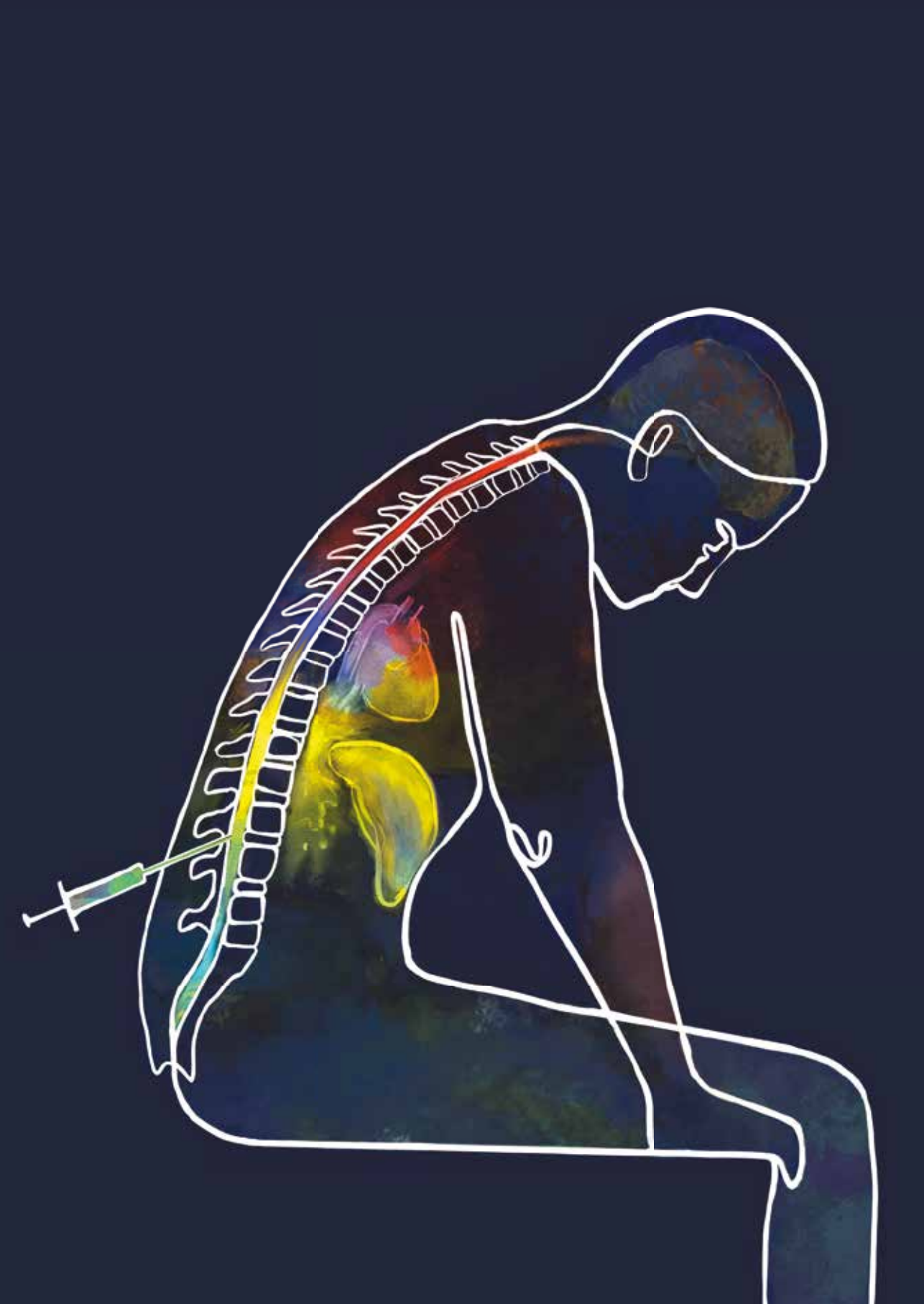

Part 1

Pharmacology of epidural analgesia

Chapter 2

Postoperative epidural analgesia after total knee arthroplasty with sufentanil 1 mcg/mL combined with ropivacaine 0.2%, ropivacaine 0.125%, or levobupivacaine 0.125%: a randomized, double-blind comparison

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Introduction

Patient-controlled epidural analgesia (PCEA) is used to provide postoperative analgesia for painful orthopedic procedures. Its benefits are avoidance of overdose, involvement of the patient in his/her own analgesic regimen, and reduction of the waiting time and "peaks and valleys" compared with physician-administered analgesics.[1] Several different amide-type local anesthetics are currently available to provide satisfactory postoperative analgesia via the epidural route. Racemic bupivacaine has traditionally been the most widely used local anesthetic for this purpose.[2,3] Ropivacaine is now frequently used as an alternative to bupivacaine. It is structurally closely related to bupivacaine and is supplied as the pure S-enantiomer.

It possesses a more favorable toxicity profile than bupivacaine, with higher thresholds for cardiotoxicity and central nervous system toxicity.[4,5] Additionally, ropivacaine tends to produce less motor blockade[6,7] which is a benefit during postoperative recovery. Levobupivacaine is the pure S-enantiomer of bupivacaine and was recently introduced into clinical practice. Preclinical studies demonstrated that both enantiomers of bupivacaine exhibit anesthetic activity, but the S-enantiomer is associated with less toxicity.[8,9] Levobupivacaine has been compared with ropivacaine and bupivacaine in epidural analgesia, but only in the perioperative and direct postoperative phase, where they produced adequate pain relief after major orthopedic surgery, with similar preservation of motor function.[10] In parturient epidural studies designed to compare the minimal effective local anesthetic concentration (MLAC), ropivacaine was determined to be 40% less potent than racemic bupivacaine.[11,12] However, controversy exists as to whether this potency difference may be extrapolated to the high end of the dose-response curve. The aim of this study is to compare the efficacy of levobupivacaine and ropivacaine in combination with sufentanil in prolonged postoperative patient-controlled epidural analgesia. The null hypothesis is the absence of a potency difference between levobupivacaine and ropivacaine at the high end of the dose response curve. An alternative hypothesis is a potency difference in favor of levobupivacaine. To explore the possible 40% potency difference suggested by previous authors, 3 different mixtures were compared: levobupivacaine 0.125%/sufentanil 1 µg/mL, ropivacaine 0.2%/sufentanil 1 µg/mL, and ropivacaine 0.125%/sufentanil 1 µg/mL.

Methods

The study was approved by the Medical Ethics Committees of the Leiden University Medical Center and the Reiner de Graaf Hospital, Delft, The Netherlands, and written informed consent was obtained from all patients. The study design was a multicenter randomized prospective double-blind comparison of ropivacaine 0.2% (group 1), ropivacaine 0.125% (group 2) and levobupivacaine 0.125% (group 3), all in combination with sufentanil 1 µg/mL.

Sixty-three patients, ASA (American Society of Anesthesiologists) Classification I to III, aged over 18 years, scheduled for total knee replacement under combined spinal-epidural anesthesia

were studied. Exclusion criteria were known hypersensitivity to amide-type local anesthetics, known hypersensitivity to opioids, known history of severe cardiovascular, renal, hepatic, neurological or psychiatric disease as judged by the investigator, known history of peripheral neuropathies, those receiving chronic analgesic therapy, any contraindication for epidural analgesia (e.g., clotting disorders, history of lumbar surgery), inability to perform a pain score, and pregnancy or lactation. After instituting routine ASA monitoring and intravenous access, the patient was placed in the sitting position and a 17-gauge epidural needle (Becton & Dickinson, Drogheda, Ireland) was introduced into the epidural space via the third lumbar interspace using the loss of resistance to saline technique. The third lumbar interspace was identified as the interspace superior to Tuffier's line (the line connecting the superior borders of the left and right crista iliaca). After identifying the epidural space, a 27-gauge Whitacre spinal needle (Becton & Dickinson) was introduced into the subarachnoid space through the epidural needle and a subarachnoid dose of 10 mg plain bupivacaine (Marcaine® 0.5% spinal [bupivacaine 20 mg/4 mL] AstraZeneca, Zoetermeer, The Netherlands) was administered. The spinal needle was then removed and an epidural catheter inserted 5 cm into the epidural space through the epidural needle. After removal of the epidural needle, the patient was placed supine. Sensory block (loss of sensation to temperature) was assessed in the anterior axillary line at 5 minute intervals using a bottle containing a frozen salt solution until the maximum level of sensory block (MLSB) had been established. MLSB was defined as no further increase during 3 consecutive measurements and >20 minutes after subarachnoid injection. Motor blockade of the lower limbs was scored on a 12 point scale, where each joint of the lower limbs (hip, knee, ankle) was scored from 0 to 2 (0, no motor block; 1, partial motor block; 2, complete motor block). Partial motor block was defined as the possibility to move the joint, but not sustainable against manual counter pressure. Motor block scores (MBS) were evaluated at 5-minute intervals until maximum motor block had been established or until 30 minutes after subarachnoid injection. After obtaining successful spinal anesthesia, a bladder catheter was inserted and surgery was allowed to proceed. Patients were randomly allocated to 1 of 3 study groups of 21 patients each using sealed envelopes and a computer-generated randomization list. During surgery patients received additional intravenous midazolam upon request, remaining easily arousable at all times. One hour after the subarachnoid dose and with the MLSB at or below T4, patients received an epidural loading dose and the time was designated as T= 0. If sensory block was above T4, sensory block was checked every 10 minutes and the epidural loading dose postponed until the block had regressed to at or below T4. Patients in groups 1 and 2 received an epidural loading dose of 10 mL ropivacaine 0.75%; patients in group 3 received 10 mL levobupivacaine 0.75%. After completion of the epidural loading dose, a PCEA device (Gemstar, Hospira, Hoofddorp, The Netherlands) with a blinded cassette was connected to the epidural catheter and started with a background infusion of 6 mL/hour, a bolus dose of 2 mL, a lock-out period of 10 minutes and a maximum of 3 bolus doses per hour. Patients in group 1 received a mixture of ropivacaine 0.2% with sufentanil 1 µg/mL, patients in group 2 received a mixture of ropivacaine 0.125% with sufentanil 1 µg/mL, and patients in group 3

received a mixture of levobupivacaine 0.125% with sufentanil 1 µg/mL. At the time of inclusion, all patients were made familiar with the PCEA device and instructed to titrate themselves to adequate pain relief (numerical rating score [NRS] of 3 or less on a scale from 0 [no pain] to 10 [intolerable pain]). The administration of the epidural loading dose and connection of the patient to the PCEA device was performed by an investigator who was not involved in subsequent data collection. NRS and MBS were recorded at 6, 12, 24, and 48 hours after administration of the epidural loading dose by blinded observers. At the same time intervals, patient satisfaction was measured using an 11 point numerical rating scale ranging from 0 (dissatisfied) to 10 (satisfied). In case of insufficient analgesia, an epidural rescue dose of 75 mg ropivacaine (groups 1 and 2) or levobupivacaine (group 3) was administered by an investigator who was aware of the treatment schedule but not involved in data collection.

Outcome variables were NRS for pain and patient satisfaction, MBS, time to first demand (TFD) of the PCEA device, bolus/demand ratio (number of granted requests/number of requests of the PCEA device), and average hourly consumption of local anesthetic and sufentanil. Average hourly local anesthetic consumption was calculated using data from the PCEA device (total infusion time and infused volume), the epidural loading dose at T = 0 plus additional top-ups administered during the study period. On the given time intervals (6, 12, 24, and 48 hours) patients were interviewed for side effects (nausea and/or vomiting and pruritus).

In the absence of relevant data, the sample size was estimated assuming 40% variability (coefficient of variation) in the number of patient-controlled requests for medication. With this assumption the sample size required to have an 80% probability of detecting a clinically relevant (40%) difference between group means (level of significance 0.05) was 21 patients per group. Sensory and motor block data, and NRS scores are reported as median (range); patient age, height and weight, TFD, bolus/demand ratio, and local anesthetic and sufentanil consumption are expressed as mean ± SD. Gender, ASA Classification, and side effects are reported as proportions.

Data were analyzed using the GraphPad InStat v.3.06 package (GraphPad Software Inc, San Diego, CA). The 2 test was used for comparison of proportions. Continuous data were analyzed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. The level of significance was set at 0.05.

Results

Sixty-three patients were studied, 21 in each group. Thirty-nine patients were studied in the Reinier de Graaf Gasthuis, 24 patients at the Leiden University Medical Center. One patient in group 3 ended the study prematurely because of catheter leakage; the data of this patient was evaluated for the first 24 hours only. Demographics of the patients were similar and are presented in Table 1.

Table 1. Patient demographics

	Group 1 Ropivacaine 0.2 % Sufentanil 1 µg/mL (n = 21)	Group2 Ropivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	Group3 Levobupivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	P
Age (years)	68,5 ± 11,9	69 ± 12,5	71,7 ± 6,9	NS
Sex (M/F)	6/15	6/15	4/17	NS
ASA Class (1/2/3)	4/15/2	3/15/3	2/15/4	NS
Weight (kg)	84,5 ± 17,7	83,8 ± 12,6	83 ± 11,7	NS
Height (cm)	166,2 ± 10,4	168 ± 8,9	165,8 ± 6,8	NS

Data are mean ± SD or number of patients. NS= no statistically significant difference.
TFD averaged 7.7 ± 4.2 hours in group 1 (ropivacaine 0.2%), 8.8 ± 5.5 hours in group 2 (ropivacaine 0.125%), and 8.3 ± 6.3 hours in group 3 (levobupivacaine 0.125%), the difference not being statistically significant. There were no significant differences between the 3 groups regarding NRS for pain and patient satisfaction, bolus/demand ratio, and MBS at any of the time intervals (Table 2).

Table 2. Pain, satisfaction, motor block scores and Bolus/Demand Ratio

	Group 1 Ropivacaine 0.2 % Sufentanil 1 µg/mL (n = 21)	Group 2 Ropivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	Group 3 Levobupivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	P
NRS Pain				
T = 6	0 (0-5)	0 (0-7)	0 (0-5)	NS
T = 12	2 (0-7)	1 (0-7)	1 (0-9)	NS
T = 24	2 (0-10)	2 (0-7)	2 (0-5)	NS
T = 48	2 (0-8)	3 (0-6)	2 (0-7)	NS
NRS Satisfaction				
T = 6	10 (7-10)	10 (6-10)	10 (8-10)	NS
T = 12	9 (2-10)	10 (6-10)	10 (3-10)	NS
T = 24	9 (1-10)	10 (4-10)	10 (3-10)	NS
T = 48	9 (1-10)	10 (4-10)	10 (6-10)	NS
Bolus/Demand	0.84 ± 0.17	0.84 ± 0.14	0.87 ± 0.22	NS
Ratio				
MBS				
T = 6	6 (0-12)	2 (0-12)	9 (0-12)	NS
T = 12	0 (0-8)	0 (0-4)	0 (0-12)	NS
T = 24	0 (0-8)	0 (0-4)	0 (0-4)	NS
T = 48	0 (0-8)	0 (0-4)	0 (0-4)	NS

NRS Pain = Numerical rating scale score for pain (ranging from 0 = no pain to 10 = very painful). NRS Satisfaction = Numerical rating scale score for patient satisfaction (ranging from 0 = highly dissatisfied to 10 = highly satisfied). Bolus/Demand Ratio: The number of granted PCEA bolus doses/bolus requests during the 48 h study period. MBS = Motor block score of the lower

limbs (ranging from 0 = no motor block to 12 = complete motor block). Data are expressed as median (range) or mean ± SD. T = 6, 12, 24 or 48: 6, 12, 24 or 48 h after administration of the epidural loading dose. NS = no statistically significant difference.

The average hourly sufentanil consumption was similar among groups. Patients in group 1 used significantly more local anesthetic as compared with patients in groups 2 and 3. Results are summarized in Table 3.

Table 3. Average local anesthetic and sufentanil consumption during 48 h

	Group 1 Ropivacaine 0.2 % Sufentanil 1 µg/mL (n = 21)	Group2 Ropivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	Group3 Levobupivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	P
Sufentanil µg/h	6.8 ± 0.7	7.1 ± 0.6	6.6 ± 0.8	NS
Local anesthetic mg/h	15.5 ± 2.0 *	10.3 ± 1.0	10.0 ± 1.6	P < 0.001

Data are mean ± SD. * Group 1 significant versus groups 2 and 3. NS: no statistically significant difference

Episodes of nausea were recorded in 43% of the patients in group 1, 38% in group 2, and 43% in group 3. Pruritus occurred in 43% of the patients in groups 1 and 2, and in 52% of the patients in group 3. Symptoms of pruritus and nausea were mild, the majority of patients requiring no treatment. Results are summarized in Table 4.

Table 4. Postoperative Nausea and vomiting (PONV) and pruritus

	Group 1 Ropivacaine 0.2 % Sufentanil 1 µg/mL (n = 21)	Group2 Ropivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	Group3 Levobupivacaine 0.125 % Sufentanil 1 µg/mL (n = 21)	P
PONV	9 (43 %)	8 (38 %)	9 (43 %)	NS
PONV M/F	2/7	1/7	2/7	NS
Pruritus	9 (43 %)	9 (43 %)	11 (52%)	NS

Data are expressed as number of patients and proportions

Discussion

This study was designed to determine the efficacy of levobupivacaine and ropivacaine in combination with sufentanil for prolonged postoperative PCEA. Under the conditions of this study all 3 combinations provided good postoperative analgesia and there were no significant differences in the outcome parameters with the exception of local anesthetic consumption. Whereas sufentanil consumption was similar, the consumption of ropivacaine was significantly higher in patients receiving ropivacaine 0.2% (group 1). The higher concentration

of ropivacaine did not result in better analgesia or a reduction in sufentanil consumption, indicating that postoperative analgesia in this setting was primarily determined by sufentanil.

Our results are in agreement with Kampe et al.[13] who found no difference in efficacy between ropivacaine 0.1% and ropivacaine 0.2%, both combined with sufentanil 1 µg/mL for postoperative analgesia after total knee replacement. Kampe et al. used a continuous epidural infusion and observed that 8 hours after initiation of the epidural infusion, patients were unable to achieve sufficient pain relief. In addition, the sample size of their study groups was small. In the present study, larger groups and PCEA technology as opposed to continuous infusion was used in an attempt to decrease sufentanil consumption with higher ropivacaine concentrations as well as evaluating the previously suggested potency difference between ropivacaine and levobupivacaine. While we did not find insufficient analgesia after 8 hours or at any other time interval, our results confirm Kampe's conclusion that when using sufentanil 1 µg/mL, an increase in ropivacaine concentration only leads to increased consumption of local anesthetic without reducing sufentanil consumption or improving the quality of analgesia. There is controversy regarding the relative potencies of ropivacaine and levobupivacaine in MLAC studies. While some observed that there is no difference in potency between levobupivacaine and racemic bupivacaine[14] others showed that ropivacaine is 40% less potent.[11,12] With these results in mind, a similar potency difference would be expected between levobupivacaine and ropivacaine. However, a recent MLAC study found levobupivacaine and ropivacaine to be equipotent.[15] This raises questions about the reliability of MLAC studies to compare potencies of local anesthetics, and about the validity of extrapolating MLAC results to the high end of the dose-response curve. We did not find a potency difference between ropivacaine and levobupivacaine. However, in view of our observation that under the conditions of our study postoperative pain relief was predominantly determined by sufentanil, it is likely that a possible potency difference has been masked by the presence of sufentanil in the epidural mixture. Adding sufentanil to a local anesthetic enhances the potency of the latter. In a labor analgesia study the MLAC of ropivacaine and levobupivaccaine was decreased with 78% by adding sufentanil 0.75 µg/mL.[16] In this study, sufentanil was used in a concentration of 1 µg/mL, which previous authors have shown effective with local anesthetics in epidural analgesia.[13,17-20] Postoperative epidural regimens aim to minimize motor block by reducing the amount of local anesthetic. Motor blockade of the lower limbs is not only a nuisance for the patient, it also interferes with early mobilization, which accelerates postoperative recovery and reduces hospital stay. In a study comparing different concentrations of ropivacaine and fentanyl, Liu et al. found that motor block was significantly more frequent with ropivacaine 0.2%21. By contrast, we observed no significant difference in motor block scores between the 3 groups. All of our patients were able to mobilize on the first postoperative day. Epidural sufentanil may contribute to postoperative nausea and vomiting (PONV), although Brodner et al. observed no increase in the incidence of PONV with increasing sufentanil doses.[22] The incidence of PONV reported by others using sufentanil 1 µg/mL in

combination with a local anesthetic varies from 10% to 20%.[19,22,23] We found a higher incidence (range 38% to 43%). This may be explained on methodological grounds: we recorded every patient mentioning 1 or more episodes of nausea and/or vomiting as PONV positive. Similarly, the incidence of pruritus in our study is higher than that reported by others. However, the severity of postoperative nausea and/or vomiting and pruritus was mild, requiring no treatment in the majority of patients.

In conclusion, all 3 solutions provided adequate postoperative pain relief. Increasing the concentration of ropivacaine from 0.125% to 2% resulted in an increase in local anesthetic consumption without improving analgesia or reducing the consumption of sufentanil. Under the conditions of our study, postoperative analgesia was predominantly determined by sufentanil.

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