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A prospective, randomized, open label, controlled study investigating the efficiency and safety of 3 different methods of rectus sheath block analgesia following midline laparotomy

Martin Purdy, MD, PhD[a,b], Mari Kinnunen, BM[b], Merja Kokki, MD, PhD[b,c], Maarit Anttila, MD, PhD[d], Matti Eskelinen, MD, PhD[b,e], Heidi Hautajärvi, BSc[f], Marko Lehtonen, PhD[g], Hannu Kokki, MD, PhD[b,c,*]

Abstract

Background: There is a controversy regarding the efficacy of rectus sheath block (RSB). The aim of the present study was to evaluate analgesic efficacy and safety of three different methods of RSB in postoperative pain management after midline laparotomy.

Methods: A prospective, randomized, controlled, open-label clinical trial with 4 parallel groups was conducted in a tertiary care hospital in Finland. A total of 57 patients undergoing midline laparotomy were randomized to the control group (n = 12) or to 1 of the 3 active RSB analgesia groups: single-dose (n = 16), repeated-doses (n = 12), or continuous infusion (n = 17). Opioid consumption with iv-patient-controlled analgesia pump was recorded, and pain scores and patients' satisfaction were surveyed on an 11-point numeric rating scale for the first 48 postoperative h. Plasma concentrations of oxycodone and levobupivacaine were analyzed. All adverse events during the hospital stay were recorded.

Results: Oxycodone consumption was less during the first 12 h in the repeated-doses and in the continuous infusion groups ($P = .07$) and in numerical values up to 48 h in the repeated-doses group. Plasma oxycodone concentrations were similar in all 4 groups. Pain scores were lower in the repeated-doses group when coughing during the first 4 h ($P = .048$ vs. control group), and at rest on the first postoperative morning ($P = .034$ vs. the other 3 groups) and at 24 h ($P = .006$ vs. the single-dose group). All plasma concentrations of levobupivacaine were safe. The patients' satisfaction was better in the repeated-doses group compared with the control group ($P = .025$). No serious or unexpected adverse events were reported.

Conclusions: RSB analgesia with repeated-doses seems to have opioid sparing efficacy, and it may enhance pain relief and patients' satisfaction after midline laparotomy.

Abbreviations: AE = adverse event, ANOVA = analysis of variance, LA = local, LC/MS/MS = liquid chromatography with triple quadrupole mass spectrometric detection, NRS = numeric rating scale, NSAID = nonsteroidal anti-inflammatory drug, PCA = patient-controlled analgesia, POP = postoperative, RSB = rectus sheath block.

Keywords: analgesia, levobupivacaine, multimodal, opioids, oxycodone, postoperative, rectus sheath block

1. Introduction

Although laparoscopic surgery has diminished the need for midline laparotomy, it is still needed in many emergency procedures and oncologic operations. Postoperative (POP) pain is the most common complaint after surgery. Pain after midline laparotomy is derived from multiple origins, for example, the abdominal wall and viscera, and from peritoneal irritation. Therefore, a single agent or pain-relieving technique is seldom sufficient for POP pain management. Thus, multimodal analgesia is usually applied. Multimodal treatment of POP pain may include nonopioid analgesics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), regional blocks, and opioids.[1]

Opioid analgesics are needed for moderate and severe pain and are especially effective for controlling nociceptive and visceral pain. However, people differ significantly in their responses to opioid analgesics. People who regularly use opioids for chronic pain conditions or who are rapid metabolizers may need larger doses to obtain sufficient analgesic efficiency. By contrast, some people are highly sensitive to opioids and are thus at increased risk of developing adverse effects.[2]

Purely opioid-based analgesic techniques are not preferred in abdominal surgery. Opioid peptide receptors are widely

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[a] Department of Surgery, Kanta-Häme Central Hospital, Hämeenlinna, [b] School of Medicine, University of Eastern Finland, [c] Department of Anesthesia and Operative Services, Kuopio University Hospital, [d] Departments of Gynecology and Oncology, Kuopio University Hospital, [e] Department of Surgery, Kuopio University Hospital, Kuopio, [f] Admescope, Ltd, Oulu, [g] School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland.

[*] Correspondence: Hannu Kokki, Kuopio University Hospital, PO Box 100, FI-70029 KYS, Finland (e-mail: hannu.kokki@uef.fi).

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distributed in the gastrointestinal tract, and so opioid analgesics impair bowel function.[3] Opioids are associated with a risk of respiratory depression, sedation, and opioid-induced hyperalgesia which may deteriorate patients' recovery.[4,5]

To overcome problems associated with higher doses of opioid analgesics, regional blocks are increasingly used.[6,7] Rectus sheath block (RSB) is an appropriate technique for midline laparotomy. Nerves enter the midline of the abdomen wall from both sides of the spinal cord roots following dermatomes Th6-L1. These nerves pass between the internal oblique and transversus abdominis muscles. They branch and communicate widely within the transversus abdominis plane and around the deep inferior epigastric artery. RSB aims to block these nerves when they pass from the posterior layer of the rectus sheath to the rectus muscle. Nerves from dermatomes Th7-L1 innervate the skin and fascia at the midline.[8]

The data are inconsistent concerning RSB's analgesic efficacy and POP opioid-sparing efficacy. Therefore, we designed the present study, which aimed to evaluate the efficacy and safety of RSB in midline laparotomy. We compared 3 different local anesthetic modalities for administering RSB. The primary objective of our study was to evaluate whether RSB has an opioid-sparing efficacy, evaluated by the rescue opioid consumption with iv-patient-controlled analgesia (PCA) pump and plasma oxycodone concentrations, in POP pain management during the first 48 POP h. The secondary outcome was to determine whether RSB could enhance patients' satisfaction with POP analgesia. The safety of RSB was determined by analyzing the plasma concentrations of levobupivacaine and by recording all adverse events (AEs) during the hospital stay. Our study's hypothesis was that RSB might decrease opioid need, enhance pain relief, and improve patients' satisfaction after midline laparotomy without compromising patient safety.

2. Materials and methods

The study design was a prospective, randomized, controlled, open-label clinical trial with 4 parallel groups. The study was conducted at Kuopio University Hospital, Kuopio, Finland, between June 2012 and December 2015. The study protocol was approved by the Research Ethics Committee of the University Hospital District of Northern Savo, Kuopio (No. 120//2011) and was registered with EudraCT (2011-005136-25) and the Clinical Trials database (NCT02869841). The Finnish Medicines Agency was notified (128/2011). The study received institutional approval and was conducted in accordance with the Declaration of Helsinki. All the subjects gave an informed consent.

Patients undergoing midline laparotomy were eligible for this study. The surgeries were gynecological, prostate, urinary bladder, and colorectal cancer operations (Table 1). Participants were enrolled by the investigators. We did not enroll patients who were aged under 18 or over 80 years, who had a body mass index <18 or over 35 kg/m^2, who were pregnant or nursing, or who had contraindications to local anesthetics or opioid analgesics or their excipients. We did not enroll patients who required a relaparotomy during the same hospital stay and those who were unable to use an iv-PCA pump.

The patients were randomized into 4 groups: single-dose, repeated-doses, continuous infiltration, and control groups. The randomization was computer generated (www.randomization.com) and was concealed until the end of the surgery using the sealed opaque envelope method.

Endotracheal anesthesia was standardized. Patients were given midazolam 1 to 2 mg i.v., and thiopental and propofol i.v. were used to induce anesthesia. Endotracheal intubation was facilitated with rocuronium 0.5 mg i.v. To ensure an adequate level of anesthesia, response entropy indexes were kept between 40 and 60 throughout the anesthesia by adjusting the inhaled desflurane concentration accordingly. Remifentanil infusion 0.5 to 2.0 μg/kg per min was used for intraoperative analgesia. The lungs were ventilated with oxygen 35% in air with positive pressure ventilation. At the end of anesthesia, muscle relaxation was reversed with sugammadex. Remifentanil infusion 0.1 mg/h was continued for the first POP hour in the recovery room. The patients' vital parameters, blood pressure, heart rate, peripheral oxygen saturation, central temperature, neuromuscular block, anesthetic gases, oxygen, and end-tidal CO_2 partial pressure were monitored continuously (Carescape B650, GE Healthcare Finland, Helsinki, Finland) during the anesthesia.

In all groups except the control group, 2 rectus sheath catheters (InfiltraLong, Pajunk, Geisingen, Germany) were inserted bilaterally before wound closure through separate skin punctures

Table 1

Patient demographics and the type of surgery (n = 57).

Variables	Control (n = 12)	Single dose (n = 16)	Repeated doses (n = 12)	Infusion (n = 17)
Age, y	67 (30–78)	61 (39–77)	69 (38–73)	59 (37–77)
BMI, kg/m^2	28 (22–34)	29* (20–35)	25 (18–31)	25 (18–32)
Sex (male/female)	4/8	5/11	3/9	2/15
ASA I/II/III/IV	1/8/3/—	—/9/6/1	—/7/5/—	2/10/5/—
Duration of surgery, min	193 (45–462)	175 (39–475)	165 (53–390)	249 (92–523)
Duration of anesthesia, min	240 (80–525)	221 (86–503)	223 (80–441)	280 (131–606)
Incision length, cm	26 (18–38)	22 (12–35)	23 (10–35)	30 (11–41)
Blood loss, mL	700 (20–2600)	300 (0–3000)	500 (0–3400)	850 (100–2750)
Type of surgery				
Gastrointestinal	4	8	5	7
Benign/cancer	1/3	4/4	2/3	4/3
Gynecological	7	6	7	10
Benign/cancer	0/7	2/4	2/5	1/9
Urological	1	2	0	0
Benign/cancer	0/1	0/2		

Data are median (minimum–maximum) or number of cases.

ASA = American Society of Anesthesiologists Physical Status Classification, BMI = body mass index.

* $P = .04$ between single dose and repeated doses (1-way analysis of variance, Bonferroni correction)/$P = .049$ Kruskall–Wallis test.

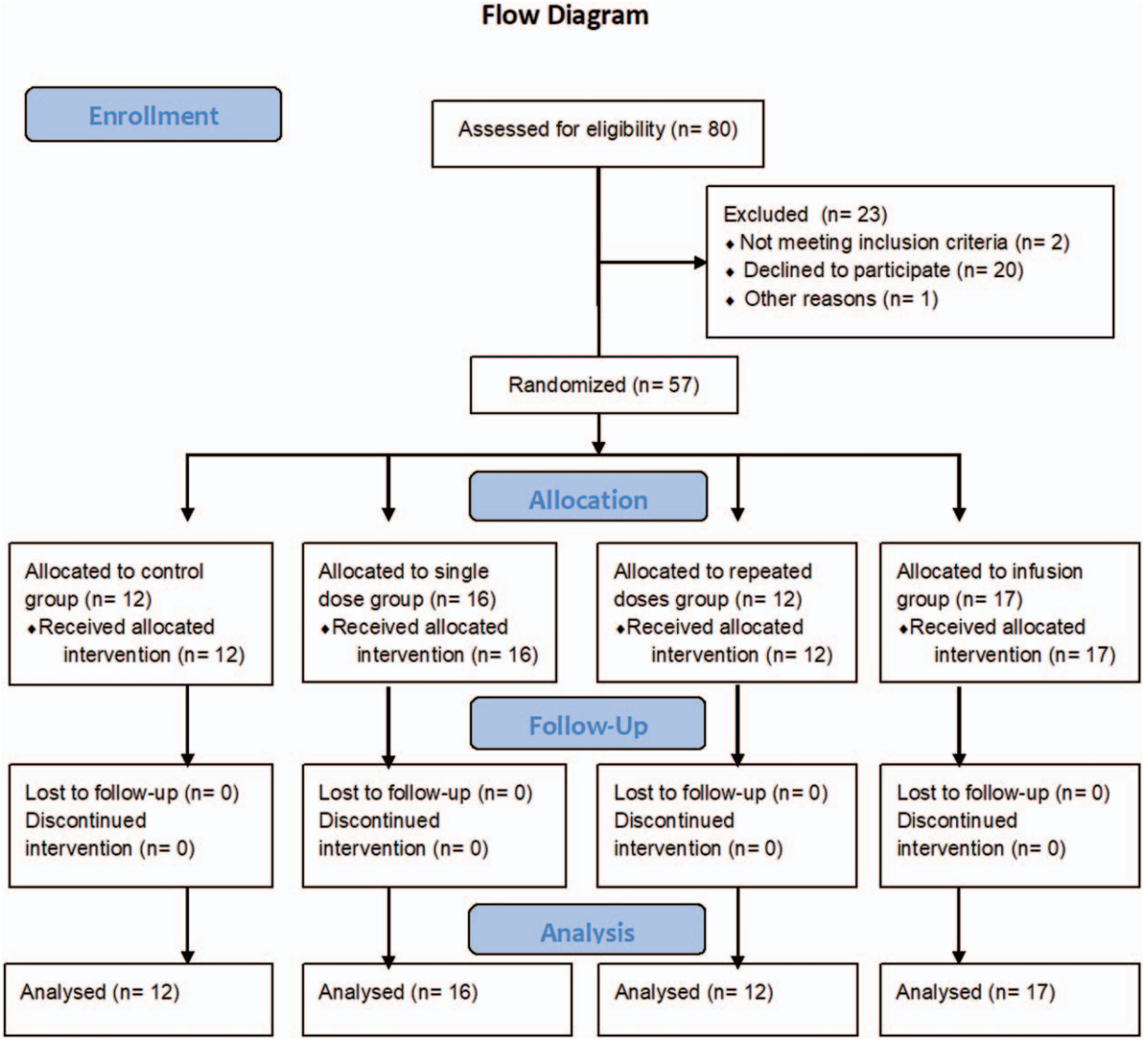

Figure 1. Flow chart.

4 or 5 cm cephalad to the incision using disposable blunt rods with sheaths. All surgeons placing the catheters were adequately trained and experienced with surgical placement of RSB catheters. Rod insertion was guided by the surgeon's hand in the abdomen to prevent posterior sheet perforations and aim toward the space between the muscle and the posterior sheath in the lateral half, where the nerves enter the muscle. All patients except those in the control group received 25 mg/20 mL levobupivacaine (Chirocaine 1.25 mg/mL AbbVie, Espoo, Finland) in both catheters for a total dose of 50 mg (flow chart, Fig. 1).

In the single-dose group, the rectus sheath catheters were removed after the first dose, and the incisions were covered with wound dressings. Similar wound dressing was used for the control group.

After the initial dose, the patients in the repeated-doses group received levobupivacaine 12.5 mg/10 mL in both catheters for a total dose of 25 mg every 4 h for the first 24 to 48 h postoperatively. In the infusion group, a local anesthetic infusion of levobupivacaine 1.25 mg/mL was started with Autofuser pumps (ACE Medical, Seoul, Korea) at a rate of 5 mL/h for both catheters for a total dose 12.5 mg/h immediately after the initial dose and was continued for 48 h or until discharge, whichever was sooner. The patients in the control group did not receive any local anesthetic injections or infiltrations.

A patient-controlled analgesia pump with a bolus dose of 2 mg of oxycodone, a lock-out interval of 10 min and a maximum dose of 12 mg/h was used for rescue analgesia. For background analgesia, the patients were given i.v. paracetamol 4 g/24 h or 3 g/24 h if the patient weighed <50 kg.

Pain at rest, dynamic pain experienced when the wound area was pressed with 20 N force and pain when coughing were measured in the recovery room and surgical ward using an 11-point numeric rating scale (NRS; 0 = no pain, 10 = most pain).[9]

Patients' satisfaction with the analgesia was determined at 48 h after surgery using the NRS (0 = totally unsatisfied, 10 = totally satisfied).

Blood samples for plasma levobupivacaine concentration analysis were taken at anesthesia induction and postoperatively 15 and 30 min and 1, 2, 4, 12, and 24 h after the first dose. In the

infusion group, blood samples were also taken for analysis 15 and 30 min and 1, 2, and 4 h after the end of the infusion. In the repeated-doses group, a blood sample was taken 2 h after the last dose. The blood samples were centrifuged at 2500g for 10 min and EDTA-blood 1000g for 15 min at 20 to 25°C and stored at −72°C until analysis.

Levobupivacaine concentrations were measured using quantitative liquid chromatography with triple quadrupole mass spectrometric detection (LC/MS/MS). The LC/MS/MS method was based on the previously published method by Hoizey et al.[10] The lower limit of quantification in plasma samples for levobupivacaine was 12.5 ng/mL. This LC/MS/MS method was selective, accurate, and precise for concentrations within a calibration range of 12.5 to 5000 ng/mL for plasma. Plasma oxycodone concentrations were analyzed in the blood samples taken at 12, 24, and 48 h after surgery, and the cumulative oxycodone consumption was recorded at the same time points. The method of oxycodone analysis has been described elsewhere.[11]

The primary outcome measure was the amount of rescue analgesic required during the 48 h postoperatively. As secondary outcomes, we recorded pain scores and patients' satisfaction. As a safety outcome, we measured plasma levobupivacaine concentrations and oxycodone concentrations 24 h after surgery, and all AEs were recorded during the hospital stay.

A sample size calculation indicated that to obtain a 30% decrease in the assumed opioid need of 20 mg (standard deviation 5) of oxycodone during the 24 h postoperatively with a desired power of 0.9 and a significance level of 0.05, 15 patients were needed in each group.

The data were entered and analyzed using IBM SPSS 23.0 (International Business Machine Corporation, Armonk, NY). To analyze the differences between groups, the Mann–Whitney *U* test was used. For continuous variables; we performed an analysis of variance (ANOVA). Group differences at different time points were tested using the Mann–Whitney *U* test and Kruskall–Wallis test, as appropriate. The results are presented as medians with range because the distributions were skewed. Data were analyzed by the intent-to-treat approach. A 2-sided *P* value of $<.05$ was considered the limit for statistical significance.

3. Results

3.1. Patient characteristics and surgical data

The patient characteristics and surgical data are presented in the Table 1.

A total of 80 patients were invited to participate, and 60 patients agreed and were randomized into the study. In 2 cases, the midline laparotomy was changed to a minimally invasive procedure. In 1 patient, the analgesia was changed to epidural block. Thus, a total of 57 patients were included in the intent-to-treat analysis, 12 in the control group, 16 in the single-dose group, 12 in the repeated-doses group, and 17 in the infusion group.

3.2. Protocol deviations

The adherence rate to the study protocol was high and data were available for all patients for entire 48 h study period. There were a few protocol deviations unlikely to affect the study results. One patient in the control group received the CYP 3A4 inductor medication carbamazepine. Her oxycodone consumption during the first 24 h was 173 mg, and her plasma oxycodone concentration 49 ng/mL, noroxycodone was 41 ng/mL, noroxymorphone was 21 ng/mL, and oxymorphone was 0.8 ng/mL. For 1 patient in the single-dose group and 1 in the control group, the PCA was stopped on the second POP afternoon due to protracted nausea. In the single-dose group, 1 patient lost the venous catheter on second POP day, and PCA was considered unnecessary and stopped at 47 h.

There were problems with rectus sheath catheters in 6 patients and with 7 catheters. One catheter of a patient in the infusion group and one of a patient in the repeated-doses group leaked. The catheters of 3 patients in the infusion group (1 patient's first catheter on the first POP morning and her second catheter at 36 h, 1 patient's catheter on the first POP evening, and 1 patient's catheter on the second POP morning) were accidentally detached. One catheter of a patient in the infusion group was constricted with sutures, leading to uneven dosing during the 48 h postoperatively.

One patient randomized to the continuous infusion group accidentally received 5 mg/mL, not 1.25 mg/mL levobupivacaine as the starting dose (40 mL, for a total dose of 200 mg), which exceeded the safety limit of 150 mg but did not prompt any local or systemic toxic reactions. Infusion was postponed for 9 h, after which she was followed and treated in compliance with the study protocol. Her recovery was uneventful and she was totally satisfied (NRS 10) with the pain treatment.

3.3. Oxycodone consumption and plasma concentrations

During the first 12 h postoperatively, oxycodone consumption was less in the infusion and repeated-doses groups than in the single-dose and control groups ($P = .07$). Thereafter the median oxycodone consumption was similar up to the 48 POP h for the 4 groups, but in numerical values it was less in the repeated-doses group (Table 2). Interindividual variation in the oxycodone consumption was high, but the variation was lowest also in the repeated-doses group. The lowest amount of iv-PCA-oxycodone was 12 mg/48 h (patient in the infusion group) and the highest 286 mg/48 h (patient in the single-dose group).

The plasma concentrations of oxycodone and its main metabolites were similar in the 4 groups (Table 3). Noroxycodone was the main metabolite detected. Plasma concentrations of oxymorphone and noroxymorphone were low in all 4 study groups.

Table 2

Cumulative oxycodone consumption (mg).

	Control (n = 12)	Single dose (n = 16)	Repeated doses (n = 12)	Infusion (n = 17)	*P*
12 h after surgery	38 (14–84)	35 (16–114)	28 (14–58)	22 (4–56)	.07
24 h after surgery	54 (22–173)	54 (26–164)	43 (26–96)	44 (10–88)	.17
48 h after surgery	75 (46–266)	97 (42–286)	64 (42–124)	84 (12–180)	.31

Data are median (minimum–maximum).

Table 3

Plasma concentrations of oxycodone (ng/mL).

	Control (n = 12)	Single dose (n = 16)	Repeated doses (n = 12)	Infusion (n = 17)	*P*
12 h after surgery	n = 0	20 (13–33), n = 9	24 (7.8–70), n = 8	13 (4.2–50), n = 8	.16
24 h after surgery	18 (10–49), n = 8	23 (13–48), n = 13	24 (8.6–37), n = 11	27 (1.6–51), n = 14	.58
48 h after surgery	n = 0	n = 0	11 (3.8–85), n = 8	19 (0.1–43), n = 7	.69

Data are median (minimum–maximum).

3.4. Pain

The pain scores are presented in Fig. 2. There were some differences across the groups in pain ratings, indicating that the repeated-doses group performed better at the first 4 h after surgery when coughing than the control group, and at rest better than other 3 groups at 12 and at 24 h better than the single-dose group (Fig. 2).

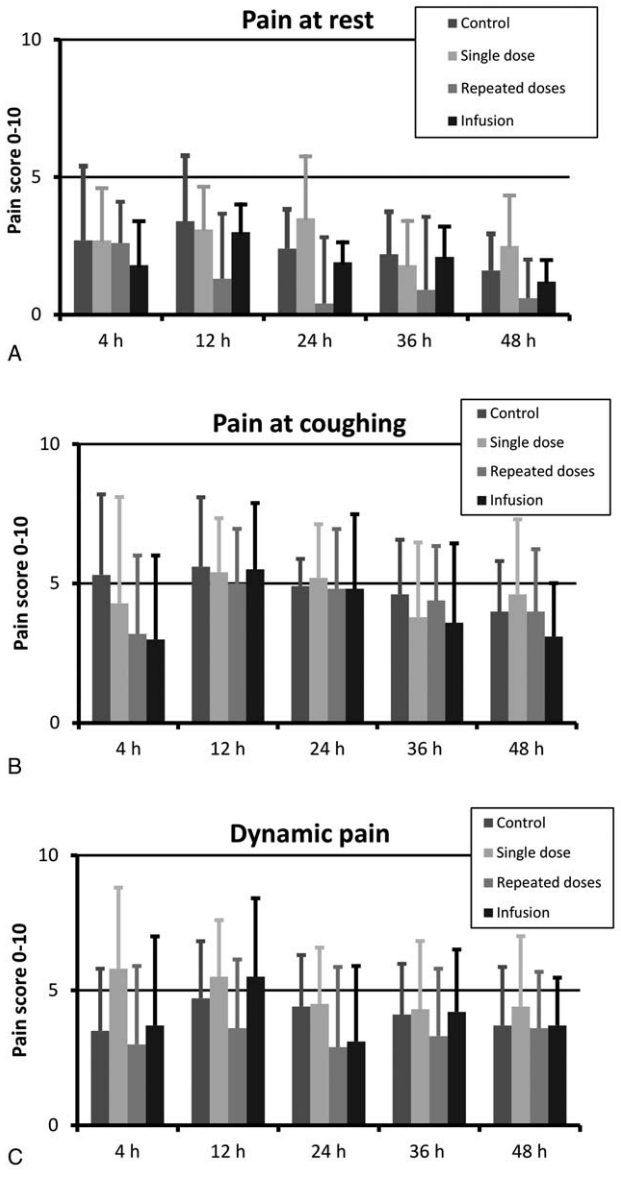

Figure 2. The median postoperative ratings for (A) pain at rest, (B) dynamic pain when coughing, and (C) dynamic pain when the wound area was pressed with 20 N force, measured with the numeric rating scale (0–10). $P = .048$ for pain at couching at 4 h (Mann–Whitney *U* test) the control group versus the repeated-doses group; $P = .034$ for pain at rest at 12 h the repeated-doses versus other 3 groups and; $P = .006$ the repeated-doses group versus the single-dose group. Data are mean, error bars are standard deviation.

3.5. Patients' satisfaction

The median of patients' satisfaction with pain management was higher in the repeated-doses group, 10 (8–10), compared with the single-dose group, 9 (4–10); the infusion group, 10 (4–10); and the control group, 8 (3–10) ($P = .025$, ANOVA).

3.6. Plasma concentrations of levobupivacaine

The levobupivacaine concentrations are presented in Fig. 3. There were no differences in the levobupivacaine concentrations between the repeated-doses and infusion groups during the first 24 POP h. The median levobupivacaine concentrations decreased from 828 (454–1865) ng/mL (at the end of 48-h infusion) to 575 (345–1629) ng/mL at 4 h after the end of infusion. All measured levobupivacaine concentrations remained <2620 ng/mL, which is considered a toxic levobupivacaine concentration.[12]

3.7. Adverse events

There were no severe or unexpected AEs during the study (Table 4). POP nausea and vomiting was the most common AE in all 4 groups. One patient in the infusion group developed pleural effusion after vast oncologic surgery with the debulking of cancer deposits in the diaphragmatic peritoneum. One patient in the repeated-doses group had a substantial bleed (3400 mL) during surgery, and she was given 2 units of packed red blood cells. Both

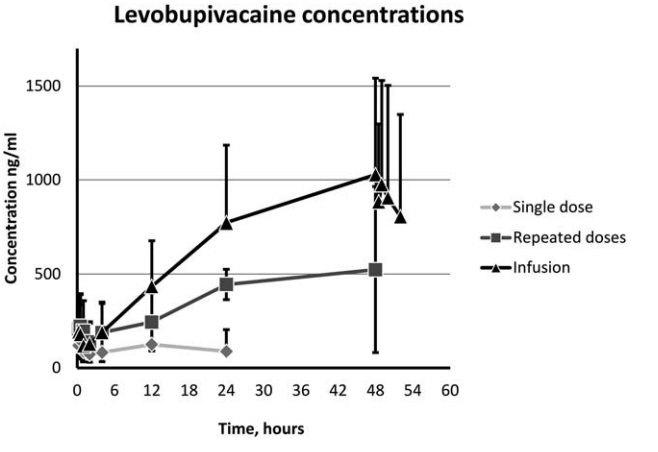

Figure 3. Plasma levobupivacaine concentrations, presented as medians and standard deviation. Time after the first dose and at cessation of infusion at 48 h. Data are mean, error bars are standard deviation.

Table 4

Adverse events during the first 48 h after surgery.

	Control (n = 12)	Single dose (n = 16)	Repeated doses (n = 12)	Infusion (n = 17)
Number of subjects with at least 1 AE	5 (42%)	14 (88%)	7 (58%)	11 (65%)
Total number of AEs	14	22	9	19
Nausea	4	8	6	10
Pain	2	3	0	0
Somnolence	2	1	0	3
Hypotension	0	1	1	1
Hypertension	0	0	1	0
Oxygen saturation < 94%	4	7	0	3
Dyspnea	0	1	0	2
Pruritus	1	1	0	0
Abnormal vision	1	0	0	0
Bloating	0	0	1	0

Data are number of cases (%).
AE = adverse event.

events were considered unrelated to the study compounds. One peripheral paresthesia was noted during the hospital stay after a long gynecologic cancer operation; it was likely caused by local nerve compression.

4. Discussion

In the present study, we evaluated RSB with different levobupivacaine administering modalities and their opioid-sparing efficacy in POP pain management in midline laparotomies. Although oxycodone consumption during the first 48 POP h was found to be similar in all 4 groups, the repeated-doses group performed better than the control and the single-dose groups during the early phase of recovery. The dynamic pain scores were low in the repeated-doses group compared with other groups at 4 h and pain scores at rest also at 12 and at 24 h after surgery compared with the control group and the single-dose group, respectively. The patients' satisfaction was also highest in the repeated-doses group.

Conflicting results regarding the efficacy of RSB have been published. Consistent with our findings, in 2 recent studies, RSB has been used as an aspect of multimodal analgesia. In both studies, RSB showed opioid-sparing efficacy and led to low pain ratings in patients undergoing laparotomy; in one of these studies, RSB was performed with repeated doses,[13] while the other study used a single dose.[14] In the repeated-doses study,[13] patients were given both paracetamol and NSAID for background analgesia compared with our study where only scheduled paracetamol was used as NSAIDs were considered contraindicated in early phase of recovery after major abdominal surgery. Contrary to these positive results as a part of multimodal approach, in Padmnabhan's study where nonopioid analgesics were not used, bilateral RSB with bupivacaine 50 mg/20 mL in both catheters at every 8 h for 48 h did not reduce opioid consumption or pain scores compared with the normal saline injections given to the control group.[15] In the present study and in Bakshis study,[13] the RSB injections were readministered at every 4 h indicating that the 8 h dosing interval in Padmanabhan's study[15] may have been too long to provide constant analgesic efficacy. In agreement with our data, Kim et al[16] found no opioid sparing efficacy and pain scores were lower only at 1 h after a single-dose RSB block but not thereafter compared with control group with no block.

Our data indicate that multimodal treatment with RSB may yield greater patients' satisfaction, although the use of opioids did not diminish that much. The importance of patients' satisfaction has been emphasized in recent years, and healthcare systems seek interventions that may improve patients care.[17] In the present study, the patients' satisfaction with pain treatment was highest among the patients who received repeated doses. High satisfaction was reported even though the pain ratings were relatively high among some of the patients in this group. An earlier study assessing patients' satisfaction with pain treatment after various surgical procedures showed that although 62% had severe POP pain, 87% were satisfied with pain management.[18] Other studies have also reported this paradoxical finding.[19,20] Patients' satisfaction depends on many factors. For example, the nature of the disease and the success of the operation may influence patients' mental status and experience of pain, as many of our patients underwent surgery due to malignancy. Repeated boluses may be associated placebo effect also. However, to support our data, experience on epidural analgesia shows that bolus doses may result in better distribution of local anesthetic solution and enhanced analgesia.[21]

Local anesthetic toxicity is a concern in all regional analgesia techniques that use large doses or continuous infusions. In the present study, neither toxic concentrations nor signs or symptoms of local anesthetic toxicity were observed. This indicates that with the doses used in our study, bilateral RSB with levobupivacaine is a safe technique. The highest levobupivacaine concentration, 1.9 μg/mL, was observed after 48 h of infusion. It decreased to 1.6 μg/mL at 4 h after the cessation of infusion. In the repeated-doses group, the median of C_{max} after the fifth injection (0.44 μg/mL) was 2 to 3 times greater than after the first injection (0.19 μg/mL). In the present study, the plasma levobupivacaine concentrations were like those reported by others. After doses were delivered to paired catheters at a total dose of 50 mg, the highest plasma levobupivacaine dose was 0.55 μg/mL; this dose is proportional to that reported for patients undergoing gynecologic laparoscopic surgery, for which C_{max} was 0.95 μg/mL at 60 min after RSB injection of levobupivacaine 2.5 mg/kg.[22] In that study, C_{max} was lower and the increase in plasma concentrations was slower after RSB than after transversus abdominis plane block. This indicates that the local anesthetic toxicity may not be as serious concern with RSB as it is with other high-volume/high-dose blocks. However, after continuous infusion, there is a risk of local anesthetic accumulation. Our data indicate that after continuous infusion, the plasma concentration of levobupivacaine decreases rather slowly, as the plasma concentration at 4 h after the cessation of infusion was

only one-fifth lower than that at the end of 48 h of infusion. This decrease is less than expected as the elimination half-life after i.v. dosing of levobupivacaine is relatively short, 1.3 h.[23] Levobupivacaine has some vasoconstrictive properties that decrease absorption from the infusion site, and rectus sheath space may perform as a reservoir for local anesthetic solutions. These may cause the slow decrease in levobupivacaine concentrations after infusion that was observed in the present study. A special concern relates to plasma concentrations of levobupivacaine when RSB is used for longer than 48 h.

Plasma oxycodone concentrations were like those reported earlier in patients undergoing cholecystectomy.[24] In the present study, the minimum effective concentrations of oxycodone were between 20 to 30 ng/mL, and the highest individual concentration was 85 ng/mL, which is like that reported previously for patients undergoing abdominal surgery.[25] The main metabolic was noroxycodone, which has weak or no μ-opioid receptor activity. Plasma concentrations of active metabolites, oxymorphone and noroxymorphone, were much lower, indicating that they probably do not contribute to the analgesic effects of oxycodone.[26]

One of the main limitations of the present study was the lack of blinding of the different dosing regimens that is challenging in this type of trials. We decided not to use an invasive placebo, thus, the control group did not undergo RSB catheterization. To conceal single-dose and control grouping, similar wound dressings were used in the same places in these 2 groups. The blinding between the control, single-dose, and repeated-doses groups could have been performed using normal saline injections. However, there have been questions regarding the use of invasive placebos with saline and their possible effects on inflammatory mediators and AEs.[27]

Another limitation of the study was the small number of patients in the different groups. Unfortunately, for logistical reasons, we could not recruit a proper sample size of patients. In addition, the selection of surgical operations varied as we had gastrointestinal, gynecological, and urological cases, which reflects the situation in normal clinical practice. However, similar midline approach into the abdominal cavity was used and similar RSB catheterization technique was used in all cases that should have decreased the variability.

Levobupivacaine 1.25 mg/mL was used in the study. Although 2.5 mg/mL concentration could have been expected to give a more prolonged effect, the 1.25 mg/mL gives at least as fast an onset of effect with less motor block. Moreover, with levobupivacaine 1.25 mg/mL solution, larger volume could be used. That could provide more extensive spread of local anestehtic in dose administration.[28] In addition, the oxycodone consumed with the iv-PCA may have disturbed the validity of pain enquiries. Some patients did not tolerate the bolus dose of 2 mg that well and some patients, on the other hand, may have benefit a larger dose than the used in this study, 2 mg/10 min. Moreover, the patients underwent different types of surgery and POP pain could be different after gastrointestinal than that after gynecological surgery. Duration of surgery varied a lot and may have affected POP pain, also. However, the distribution of surgical cases and duration of surgeries was similar across the groups.

Our data could be applied to clinical practice. Data indicate that bilateral RSB with either repeated doses of 10 mL to each side at every 4 h or as a continuous infusion of 5 mL/h for both sides with levobupivacaine 1.25 mg/mL is a feasible option for POP pain management as a part of multimodal pain management protocol after midline laparotomy. With this approach extensive doses of opioids can be avoided and patients' satisfaction to pain treatment could be improved.

In conclusion, pain relief and patients' satisfaction were superior in the repeated-doses RSB group. Early opioid consumption for rescue analgesia was less in the repeated-doses and continuous infusion groups than that in the single bolus and control groups. Some very high oxycodone requirements were found in the single-dose and control groups but not in the repeated-doses or continuous infusion groups. The use of RSB may be a feasible aspect of multimodal analgesia treatment after midline laparotomy.

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