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Original Article

Ultrasound-guided subcostal transversus abdominis plane blocks with liposomal bupivacaine vs. non-liposomal bupivacaine for postoperative pain control after laparoscopic hand-assisted donor nephrectomy: a prospective randomised observer-blinded study

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Summary

We compared the effect of subcostal transversus abdominis plane (TAP) block with liposomal bupivacaine to TAP block with non-liposomal bupivacaine on postoperative maximal pain scores in patients undergoing donor nephrectomy. Sixty patients were prospectively randomly assigned to receive ultrasound-guided bilateral TAPs with either 1.3% liposomal bupivacaine and normal saline or 0.25% non-liposomal bupivacaine with adrenaline. There was a significant decrease in maximal pain scores in the liposomal bupivacaine TAP group when compared with the non-liposomal bupivacaine group median (IQR [range]), 24–48 h after injection, 5 (3.0–5.2 [0–10]) vs. 6 (4.5–7.0 [1—9]) p = 0.009; 48–72 h after injection, 3 (2.0–5.0 [0–8]) vs. 5 (3.0–7.0 [0–10]) p = 0.02; and in opioid use 48–72 h after injection, mean (SD) μg equivalents of fentanyl 105 (97) vs. 182 (162) p = 0.03. Liposomal bupivacaine via subcostal TAP infiltration provided superior analgesia up to 72 h after injection when compared with non-liposomal bupivacaine.

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Introduction

Laparoscopic live donor nephrectomy is preferred to open nephrectomy at most centres. It is associated with less pain, shorter recovery and shorter hospital stay, although it has a similar incidence of perioperative complications [1]. We typically use the hand-assisted laparoscopic technique as it is easier to teach, offers increased intra-operative safety and requires fewer trocar sites while requiring a similar size (albeit differently located) kidney extraction incision [2, 3]. The extraction incision is supra-umbilical in the midline at dermatomes T6-T9 and is 5–8 cm in length. Before this study, we used either liposomal bupivacaine or non-liposomal bupivacaine in transversus abdominis plane (TAP) blocks for patients undergoing donor nephrectomy procedures.

In the postoperative period, pain control is often treated primarily with parenteral opioids and/or epidural analgesia. Both are associated with risks. Transversus abdominis plane block is a novel procedure that

has been shown to reduce postoperative pain and morphine requirements in the first 24 h after midline abdominal surgery [4]. Transversus abdominis plane blocks using non-liposomal bupivacaine in laparoscopic donor nephrectomy have been associated with a reduction in pain scores and opioid use in the first 24 h following surgery, but not at 48 h [5]. When used as a component of an enhanced recovery protocol for donor nephrectomy, TAP blocks have been associated with a reduction in postoperative opioid use and shorter hospital length of stay [6].

Liposomal bupivacaine (EXPAREL®; Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA) is a multivesicular form of bupivacaine that has been shown to provide postsurgical analgesia and reduced opioid use up to 72 h postoperatively in haemorrhoidectomy and bunionectomy following local infiltration at the surgical site. Bupivacaine lies within microscopic spherical liposomes; as some of these liposomes break open, they release 1.3% bupivacaine into the area where the liposomal bupivacaine has been injected. The remaining liposomes reorganise and continue to break open, releasing 1.3% bupivacaine over several days [7].

The primary objective of our study was to compare the effect of TAP blocks using liposomal bupivacaine with TAP blocks using non-liposomal bupivacaine on maximal pain scores up to 72 h after surgery. Secondary objectives were to compare effects on opioid use, nausea and vomiting, and length of stay.

Methods

Following University of Minnesota Institutional Review Board approval, all consecutive donor nephrectomy patients were screened for enrolment between May 2013 and July 2014. Patient exclusion criteria were history of chronic pain, inability to speak English, weight less than 60 kg or opioid use < 3 weeks before surgery. After giving informed consent, patients were randomly assigned (by blindly choosing random numbers from a closed envelope) to undergo TAP block with either 1.3% liposomal bupivacaine or non-liposomal 0.25% bupivacaine with adrenaline 1:200,000 (which was the standard for TAP blocks at our institution). All blocks were performed or supervised by one of four anaesthetists trained in the TAP infiltration procedure. Those performing the block were not blinded to the local anaesthetic used, but patients and research personnel were blinded.

Patients were placed in the supine position following insertion of a peripheral intravenous catheter. Sedation (1–2 mg of intravenous midazolam) and/or analgesia (50–100 μg of fentanyl) were provided before TAP block placement at the discretion of the attending anaesthesiologist. The abdominal wall on the side of the nephrectomy was prepped with a chlorhexidine gluconate and isopropyl alcohol prep stick (CareFusion, Leawood, KS, USA) and allowed to dry. A subcostal TAP block was performed as previously described by Hebbard [8]. A linear array transducer probe (6–13 MHz) in multibeam mode was connected to a portable ultrasound unit and covered in a sterile sheath. The probe was positioned on the abdominal wall at the xiphoid cartilage and moved laterally along the subcostal ridge to obtain a transverse view of the abdominal wall layers, listed from superficial to deep: skin; subcutaneous fat; rectus sheath; transversus abdominis; and peritoneal cavity. When the rectus aponeurosis was identified with ultrasound, a skin wheal was made with 2% lidocaine (1–3 ml) and a 100-mm, 22-gauge needle advanced from a medial to lateral direction using the in-plane technique with ultrasound real-time assessment. The progression of the needle, visible as a bright hyperechoic line, was assessed with direct ultrasonography. The injection site was beneath the fascia covering of the transversus abdominis muscle. When the needle tip was correctly located within the targeted plane, an image was saved into the patient record and the local anaesthetic injected with intermittent aspiration. Correct placement of the needle was confirmed by the appearance of an oval-shaped dark shadow, indicating expansion of tissues caused by the local anaesthetic solution between the aponeurosis of the rectus sheath and the transversus abdominis muscle. A total dose of 30 ml was deposited in this plane and the procedure repeated on the contralateral side, giving a total volume of 60 ml. If the patient was randomly assigned to the liposomal bupivacaine group, they received a total 30 ml volume of solution, comprising 20 ml of normal saline and 10 ml of 1.3% liposomal bupivacaine. If the patient was randomly assigned to the non-liposomal bupivacaine group,

30 ml of 0.25% bupivacaine with adrenaline 1:200,000 was used.

Between 15 min to 1 h after injection, the donor nephrectomy procedure was performed under general anaesthesia. The extraction incision was as previously described. Intra-operative pain control was at the discretion of the attending anaesthetist or certified registered nurse anaesthetist (CRNA). Intra-operative opioid use was recorded. Once the patient reached the post-anaesthesia care unit (PACU), opioid and ketorolac use, maximum and minimum pain scores on a 0–10 numerical rating scale (NRS), time to first opioid given and time spent in PACU were all recorded. Time spent in PACU was defined as the time from when patients entered PACU to when they met discharge criteria for transfer from the first phase of PACU [9]. The first phase of PACU was defined as the time period where the focus is on patient recovery from anaesthesia and stabilisation to the inpatient setting. Discharge criteria from the first phase of PACU were determined by a PACU nurse when the patient scored an 8 or higher on the Aldrete scoring system and had tolerable pain control [10]. A PACU nurse who was blinded to the TAP local anaesthetic used recorded all PACU data. Maximal pain scores were defined as pain with activity, or the highest pain score experienced by the patient if they were unable to determine their pain with activity. Minimum pain scores were defined as pain at rest, either lying down or sitting. Pain scores, opioid and ketorolac use, and presence or absence of nausea/vomiting were recorded at 24 h, 48 h and 72 h by the regional anaesthesia resident, regional anaesthesia nurse practitioner or ward nurse, all of whom were blinded to the TAP block medication used. The highest and lowest pain scores for each patient were recorded during the specific time period. The nurse practitioner or resident assessed pain scores once per time period, and the ward nurse assessed multiple times per time period. On each shift (three per day), the bedside nurses asked the patients if they experienced symptoms such as metallic taste in mouth, ringing in ears or numbness in lips that may indicate local anaesthetic toxicity. This was then recorded on the nursing flow sheet. The surgical team (as per standardised order sets) ordered all postoperative opioid and non-opioid pain medications. Both intravenous or oral opioids and ketorolac were ordered to be given by nurses when patients experienced moderate to severe postoperative pain. Intravenous opioids used were fentanyl, hydromorphone or morphine, and oral opioids were hydromorphone, hydrocodone or oxycodone. All opioids were converted into fentanyl equivalents for comparison. Other recorded variables were: total opioid dose; surgery length (defined as anaesthesia start to anaesthesia end, as recorded by the CRNA or anaesthesiology resident); and total length of stay (as measured from the beginning of the first phase until the patient was ready to be discharged home). The surgical team (blinded to treatment group) made the determination of when the patient was ready to discharge according to local guidelines. The patient had to be able to void urine after urinary catheter removal, tolerate at least a liquid diet, not require intravenous anti-emetics and feel comfortable with their pain control before discharge. Opioid use from 0–24 h included only those opioids that were administered after the patient was discharged from the PACU. Nausea and vomiting were recorded if the patient answered 'yes' when asked by the nurse practitioner or resident if they had received anti-emetics during the postoperative period, or if the patient notes recorded that the patient had experienced nausea or vomiting.

Based on institutional data of pain scores in patients who received TAP infiltration with bupivacaine for donor nephrectomy, we determined that a total of 18 patients per treatment arm would be needed to achieve 80% power with 0.05 α. We assumed up to 20% patients might be lost to follow-up, 10% converted to open surgery or change in surgical site and 10% might be non-compliant, so 30 patients were enrolled in each study arm. For continuous variables, a Student's t-test was performed. Length of stay, pain scores, and time to first opioid were analysed using the Mann–Whitney U-test. GraphPad Prism Software (version 6.0b, La Jolla, CA, USA) was used for statistical analysis. A two-sided $p < 0.05$ was considered statistically significant.

Results

Eighty-eight patients underwent laparoscopic hand-assisted donor nephrectomy from May 2013 to July 2014 at the University of Minnesota Medical Centre

(Fig. 1). Twenty-eight patients did not meet inclusion criteria or declined to participate in the study. Sixty patients were enrolled (30 in the liposomal bupivacaine group and 30 in the non-liposomal bupivacaine group). One patient in the non-liposomal bupivacaine group had a transverse Pfannenstiel incision and was withdrawn from the study, so 29 patients in the non-liposomal bupivacaine group and 30 patients in the liposomal group were analysed. The baseline characteristics of both groups were similar (Table 1). Table 2 contains the data obtained in the PACU, and the results were similar between the two groups.

Maximal pain scores median (IQR [range]) were significantly lower in the liposomal bupivacaine group compared with the bupivacaine group at 24–48 h. 5 (3.0–5.2 [0–10]) vs. 6 (4.5–7.0 [1–9]), p = 0.009; and 48–72 h, 3 (2.0–5.0 (0–8]) vs. 5 (3.0–7.0 [0–10]), p = 0.02 (Fig. 2). In addition, we observed a significant decrease in opioid use (μg of fentanyl equivalents) in the liposomal bupivacaine group compared with the bupivacaine group at 48–72 h after injection, mean (SD) 105 (97) μg vs. 182 (162) μg p = 0.03 (Fig. 3), with no difference between the two groups at 0–24 h and 24–48 h after injection. The minimum pain scores were similar in both groups at all time periods. All

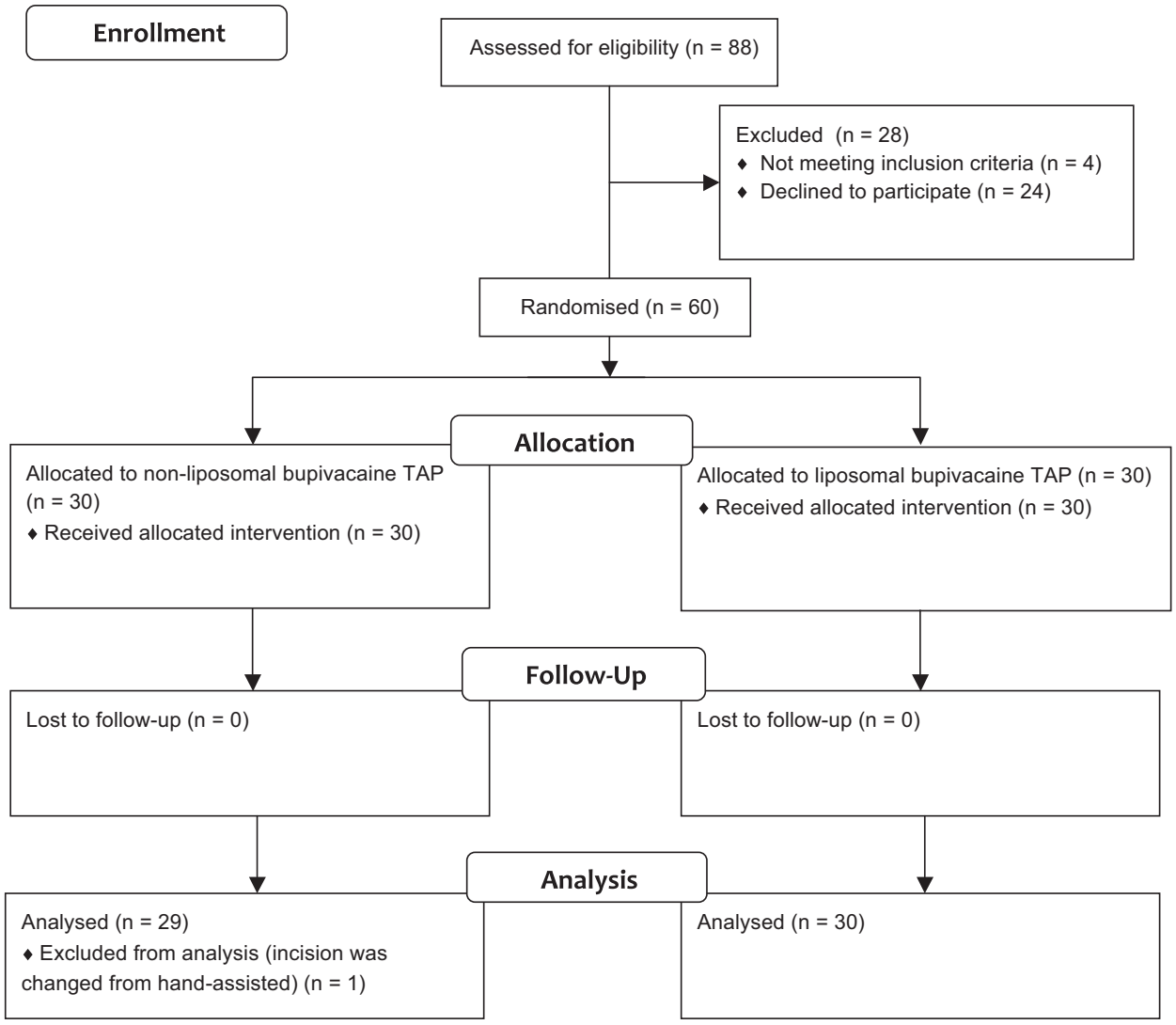

Figure 1 CONSORT diagram of patient enrolment for the prospective randomised study. TAP, transversus abdominis plane.

Table 1 Baseline and intra-operative characteristics of patients who received either liposomal bupivacaine or non-liposomal bupivacaine for transversus abdominis plane infiltration. Values are mean (SD) or number.

	Liposomal bupivacaine n = 30	Non-liposomal bupivacaine n = 29	p value
Age; y	41.0 (12.5)	38.0 (12.6)	
Weight; kg	78.7 (12.3)	75.5 (15.5)	
Sex; n			
Male	14	10	
Duration of surgery; min	279 (57)	256 (61)	0.2
Intra-operative opioids; μg fentanyl equivalent	404 (184)	352 (144)	0.2

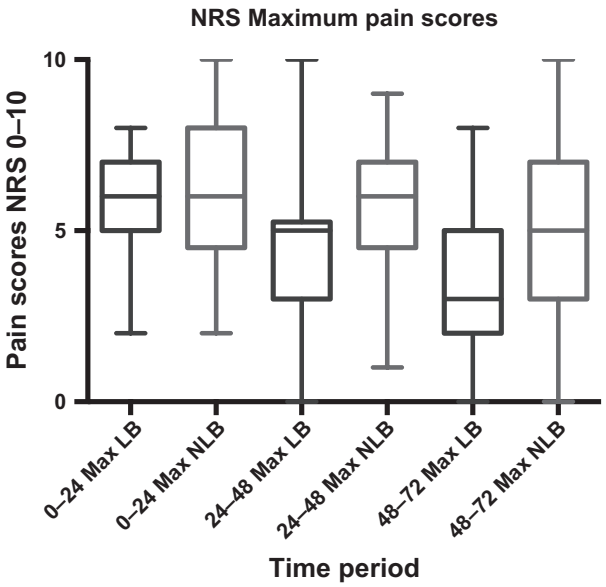

Figure 2 Maximal pain scores (numeric rating scale (NRS) 0–10) in patients receiving transversus abdominis plane infiltration with liposomal bupivacaine (LB) or non-liposomal bupivacaine (NLB). There is a significant difference between LB and NLB at 24–48 h and 48–72 h.

patients enrolled in the study received ketorolac during the first 72 h postoperatively. There was no difference between the two treatment groups in ketorolac use at all postoperative time points (Table 3). Nausea and vomiting within 72 h of injection was significantly less for patients in the liposomal bupivacaine group compared with the non-liposomal bupivacaine group (7 patients vs. 15 patients, respectively, p = 0.03). Median length of stay in hours was significantly shorter in the liposomal bupivacaine group median (IQR [range]) 67.7 (55.4–77.8 [47.1–104.1]) vs. bupivacaine group 78.1 (62.8–82.3 [52.5–103.6]), p = 0.02.

Discussion

Our findings suggest that patients who had pre-operative TAP blocks with liposomal bupivacaine experienced decreased maximal pain scores at 24–48 h and 48–72 h, and decreased opioid use at 48–72 h when compared with TAP blocks with non-liposomal bupivacaine, which contributed to a decreased length of stay and decreased incidence of nausea and vomiting. There were no differences between the two groups in any of the PACU measurements or during the first 24 h after injection, suggesting that both liposomal bupivacaine TAP blocks and non-liposomal bupivacaine TAP blocks provided similar levels of analgesia in the first 24 h after injection.

These results show that a TAP block with liposomal bupivacaine offers long-lasting analgesia

Table 2 Characteristics of patients in the post-anaesthesia care unit (PACU) who received transversus abdominis plane infiltration with either liposomal bupivacaine or non-liposomal bupivacaine. Values are mean (SD) or median (IQR [range]).

	Liposomal bupivacaine n = 30	Non-liposomal bupivacaine n = 29	p value
Minutes to first opioid; min	20.0 (14.3–43.8 [5.0–210.0])	23.0 (13.5–56.0 [2.0–1373.0])	0.6
Ketorolac; mg	9.0 (7.4)	10.8 (9.7)	0.4
Opioids; μg fentanyl eq.	151 (90)	129 (132)	0.5
Maximum pain; NRS 0–10	6 (4–7 [0–9])	6 (5–9 [0–10])	0.4
Minimum pain; NRS 0–10	3 (2.0–4 [0–6])	3 (0–4 [0–8])	0.4
Time in PACU; min	110 (32)	112 (32)	0.8

NRS, numeric rating scale.

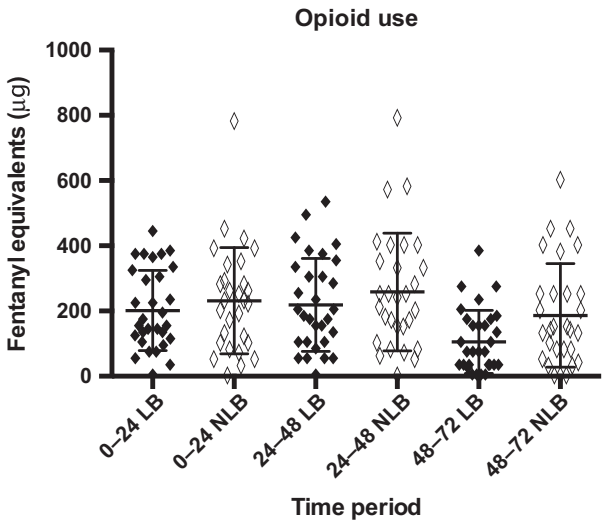

Figure 3 Postoperative opioid use (fentanyl equivalents in micrograms) in patients receiving transversus abdominis plane infiltration with liposomal bupivacaine (LB) or non-liposomal bupivacaine (NLB). Error bars are SD. There is a significant difference between LB and NLB at 48–72 h.

when compared with a TAP with non-liposomal bupivacaine. This is similar to our previously reported findings comparing TAP block with liposomal bupivacaine to a TAP block with non-liposomal bupivacaine during robotic hysterectomy surgery [11]. It costs £649 ($950, €847) per day for a medical/surgical bed at the University of Minnesota. A decrease in median length of stay of 10.4 h results in a cost savings of £282 ($412, €367) per patient, which results in a cost savings of greater than the £215 ($315, €281) cost per vial of liposomal bupivacaine. The decrease in length of stay could be related to improved pain control and/or less nausea and vomiting in the liposomal bupivacaine group. Several studies have demonstrated the cost savings of decreased opioid-induced nausea and vomiting, whether by decreasing length of stay, decreasing use of anti-emetic medications or decreasing the need to switch to alternative pain medications [12, 13].

While several studies have compared TAP blocks with bupivacaine or ropivacaine with saline, most have showed a limited duration of action (< 24 h) of the local anaesthetic. Previous investigators have found that TAP infiltration with bupivacaine in patients undergoing laparoscopic donor nephrectomy was associated with lower pain scores and opioid use when compared with placebo. However, the difference in opioid use was only significant up to 6 h postoperatively [5]. Another study comparing bupivacaine with placebo in laparoscopic donor nephrectomy showed that those with bupivacaine TAP had longer time to first analgesic, lower VAS pain scores and lower tramadol use [14]. Tanggaard et al. compared the use of ropivacaine with saline in pre-operative infiltration into the TAP plane, which showed decreased pain scores up to 12 h after injection, but no differences in opioid consumption [15]. In contrast to the studies listed above, a study by Gulyam Kuruba et al. that examined the use of levobupivacaine in a TAP injection failed to show any effects on pain scores or opioid consumption up to 24 h after renal transplantation [16].

In addition to our previous study, which showed decreased total opioids in the first 72 h after robotic

Table 3 Postoperative characteristics of patients who received transversus abdominis plane infiltration with either liposomal bupivacaine or non-liposomal bupivacaine in the first 3 d after surgery. Values are mean (SD), median (IQR [range]) or number (proportion).

	Liposomal bupivacaine n = 30	Non-liposomal bupivacaine n = 29	p value
Ketorolac 0–24 h; mg	32.5 (15.3)	36.4 (13.8)	0.31
Ketorolac 24–48 h; mg	44.5 (23.4)	51.7 (17.7)	0.19
Ketorolac 48–72 h; mg	19.0 (21.2)	29.3 (26.9)	0.11
Nausea/vomiting	7 (23%)	15 (52%)	0.03
Length of stay; h	67.7 (55.4–77.8 [47.1–104.1])	78.1 (62.8–82.3 52.5–103.6])	0.02
Minimum pain score 0–24 h; NRS	2.5 (1–3 [0–5])	2 (1–3 [0–7])	0.95
Minimum pain score 24–48 h; NRS	2 (0–3 [0–4])	3 (0–4 [0–5])	0.21
Minimum pain score 48–72 h; NRS	1 (0–2 [0–3])	1 (0–3 [0–4])	0.21

NRS, numerical rating scale.

hysterectomy [11], other studies have evaluated liposomal bupivacaine for TAP infiltration. Feierman et al. showed in a small prospective cohort that liposomal bupivacaine could be used in a TAP infiltration without adverse events [17]. Likewise, in our study, there were no indications of local anaesthetic toxicity in either study group.

The use of liposomal bupivacaine in other infiltration techniques has been successful when combined with a multimodal analgesic regimen [18, 19]. Cohen showed that addition of liposomal bupivacaine infiltration to a multimodal technique decreased postoperative opioid use, length of stay and cost of hospitalisation [18]. Candiotti et al. also demonstrated that liposomal bupivacaine infiltrated as part of a multimodal technique decreased opioids and length of stay when compared with the local standard of care [19]. In addition to studies examining efficacy, a study by Damjanovska et al. demonstrated that there were no histological changes when liposomal bupivacaine was injected peri- or intraneurally compared with saline injection in an animal model [20].

The main limitation of our study is that the anaesthetist performing the TAP block was not blinded to the study group assignment, which may have influenced intra-operative and PACU analgesic administration. However, all other staff involved in patient care and data collection were blinded to the study group assignment. Another potential weakness is that the postoperative opioid and ketorolac doses were administered on an as-needed basis (and not scheduled or according to a protocol). In addition, we did not assess patient satisfaction as an outcome for this study, which may have provided additional clinical value to our observed outcomes. We acknowledge that additional randomised multicentre trials are needed to confirm these results in a larger number of patients in order to eliminate potential centre effects and Type 2 errors. Furthermore, our technique of subcostal TAP injection only allowed for coverage of incisional pain, with limited coverage of visceral pain owing to lack of posterior and paravertebral local anaesthetic spread using this technique. Utilising a more posterior approach as described in the paper by Carney et al. could ensure more paravertebral spread, increased duration of action and better visceral coverage [21].

Our patients did receive different total dosages of bupivacaine. Those in the liposomal bupivacaine group received a dose of 266 mg bupivacaine. This is because bupivacaine in the liposomes is 1.3%. Those who received 0.25% bupivacaine received 150 mg of bupivacaine hydrochloride. As the bupivacaine used in the liposomal formulation is not the same as bupivacaine hydrochloride, it is difficult to determine if this dose difference had any effect on the outcomes presented. Our decision to dilute the liposomal bupivacaine with normal saline to 30 ml per TAP block was based on our previous experience that smaller injected volumes resulted in suboptimal pain relief. We believe that because liposomal bupivacaine is more viscous, it spreads less in tissues, and diluting the medication ensures better spread in the transversus abdominis plane.

In summary, this prospective randomised controlled trial showed that liposomal bupivacaine administered via subcostal TAP infiltration provided superior analgesia up to 72 h after injection when compared with non-liposomal bupivacaine. Furthermore, patients in the liposomal bupivacaine study group had less nausea and vomiting and decreased median length of stay than patients in the non-liposomal bupivacaine study group. Future studies could focus on comparisons between liposomal bupivacaine and other long-acting local anaesthetics that are currently in development [22].

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Competing interests

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