A randomized comparative study of ultrasound-guided quadratus lumborum block versus transversus abdominis plane block in patients undergoing paraumbilical hernia repair

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Background

The pain following abdominal surgeries is one of the main problems faced by patients postoperatively and leads to immobility and prolong hospital stay. In the study, we compare the efficacy of two modalities for controlling the pain postoperatively after paraumbilical pain hernia repair.

Aim

To compare the analgesic effect between ultrasound-guided quadratus lumborum block (QLB) and transversus abdominis plane (TAP) block in patients undergoing paraumbilical hernia repair regarding pain control by measuring visual analog scale (VAS) score as the primary outcome. Vital data [systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), and heart rate (HR)] measured from postanesthetic care unit (PACU) till 24 h postoperatively, the total amount of rescue analgesia, and the time to first analgesia request in the 24 h postoperatively were the secondary outcomes.

Patients and methods

A double-armed prospective randomized comparative study was done in the hospital of Ain Shams University (El-Demerdash Hospital) on 46 patients undergoing paraumbilical hernia repair. The patients were randomly and equally distributed into two main groups. They all received general anesthesia, and after finishing the surgery before extubation, the block was performed under aseptic technique. Group QL (23 patients) received ultrasound-guided bilateral QLB using bupivacaine 0.25% as injection at a volume of 0.2 ml/kg per side, and group TAP (23 patients) received ultrasound-guided bilateral TAP block using bupivacaine 0.25% as injection at a volume of 0.2 ml/kg per side.

Measurements

The primary outcome was the measurement of VAS score, and secondary outcomes were measurement of vital data (SBP, DBP, MABP, and HR) from PACU till 24h postoperatively at PACU, 30 min in PACU, and then 2, 4, 8, 12, and 24h postoperatively; the total amount of rescue analgesia; and the time to first analgesia request in the 24h after operation.

Results

A significant difference was found between the two groups regarding the VAS score, with P value less than 0.001, as well as vital data (SBP, DBP, MABP, and HR) measured at PACU, 30 min in PACU, and then 2, 4, 8, 12, and 24 h postoperatively, with P value less than 0.001. The total amount of pethidine requested as a rescue analgesia was less in the QL group than the TAP group, with P value less than 0.001, and the time to first analgesia request was longer in the QL group than the TAP group, with P value less than 0.001.

Conclusion

QLB is more effective for controlling the pain following paraumbilical hernia repair than TAP block and requires less opioids postoperatively as a rescue analgesia.

Keywords:

paraumbilical hernia, postoperative pain, quadratus lumborum block, transversus abdominis plane, ultrasound

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Background

Effective early postoperative analgesia decreases the incidence of chronic postoperative pain. Regional anesthesia allows for reducing postoperative opioid requirements with subsequent opioid-related adverse

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effects, complications, and incidence of chronic postoperative pain. Advances such as ultrasonography have led to regional anesthesia becoming a rapidly developing field [1,2].

There are many techniques available for pain control after operations, two of which include transversus abdominis plane (TAP) block and quadratus lumborum block (QLB). The TAP block technique was done by introducing local anesthesia into the neurovascular plane between the internal oblique and transversus abdominis muscles [3].

Blanco introduced the OLB as a variation of the TAP block, suggesting it to be a confidential technique for reducing pain following surgeries of the abdomen. The TAP block is a block of the anterior abdominal wall and has massive interindividual variability in its distribution of block and coverage [4,5].

The QLB is a block of the posterior abdominal wall where local anesthetics are injected near to the anterolateral aspect of the quadratus lumborum muscle and its fascia. This block is now used for a large number of patients undergoing abdominal surgery [6,7].

The visceral block will provide better postoperative pain relief that allows early ambulation. The TAP block gives good somatic analgesia with little or no visceral block, whereas the posterior technique, which includes injecting local anesthetic near to the quadratus lumborum muscle, produces good visceral analgesia [8]. We assume that the QLB could have sufficient analgesic effect and longer duration of action in comparison with the TAP plane block.

Aim

The aim was to compare the analgesic effect between ultrasound-guided QLB and TAP block in patients undergoing paraumbilical hernia repair regarding pain control by measuring visual analog scale (VAS) scores as a primary outcome. Vital data [systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), and heart rate (HR)] measured from postanesthetic care unit (PACU) till 24h postoperatively (PACU, 30 min in PACU, and then 2, 4, 8, 12, and 24 h postoperatively), the total amount of rescue analgesia, and the time to first analgesia request in the 24h postoperatively are the secondary outcomes.

Patients and methods

The study was done at Ain Shams University Hospitals within 15 months with approval from the Departmental Research Ethics Committee (REC), with identification no. FMASU MD 245/202/2021, and approval of Pan African Clinical Trial Registry, with identification no. PACTR202110586403919. An informed consent was taken from the patients. A total of 50 patients were enrolled in the study with two patients had a difficult sonoanatomy for QLB and one patient had a difficult sonoanatomy for TAP block and one patient refused to complete the study (Fig. 1). A total of 46 patients, with age ranged between 20 and 60 years, American Society of Anesthesiology (ASA) classes 1 and 2, underwent elective paraumbilical hernia repair with general anesthesia. Patients were randomly distributed into two equal groups using a random number table and the use of a closed envelopes technique and were subjected to a comparative study. Group QLB (23 patients) received ultrasound-guided bilateral QLB, and bupivacaine 0.25% was used for injection with a volume of 0.2 ml/kg per side, and group TAP (23 patients) received ultrasound-guided bilateral TAP block, and bupivacaine 0.25% was used for injection with a volume of 0.2 ml/kg per side.

Sample size

A total of 46 patients were assumed to have an effect size for pain score at either 2, 4, and 6h of 1, so a sample size of 23 patients in each group would be enough to detect good effect at 0.05 alpha error and 0.9 power of the test [9].

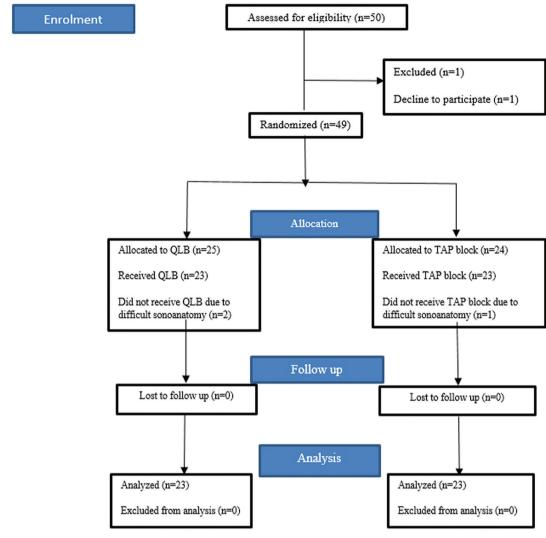
Exclusion criteria were presence of allergy to drugs used in the study, contraindications to perform a regional anesthesia (as a coagulopathy and local infection), impairment, renal dysfunction, hepatic psychiatric disorder, pregnancy, morbid obesity, and refusing to give written informed consent.

Preoperative assessment was done, which included full history taking, number of fasting hours, general examination, and routine preoperative laboratory investigations including complete blood count, liver function tests, kidney function tests, prothrombin time, and activated partial thromboplastin time.

Patients were educated about the VAS at the preoperative assessment. VAS is a 10-cm line, with 0 at one pole, meaning pain not present, and 10 at the other pole, meaning severe pain. All patients were kept nil orally for 8h before the surgical procedure.

Intraoperative monitoring was done through ECG, noninvasive blood pressure, and pulse oximetry. Preoperative vital data systolic (SBP, DBP, and MBP), HR, and arterial oxygen saturation were recorded. Intravenous cannula was applied, and intravenous fluids were given.

Figure 1



Participant flow diagram.

General anesthesia was used, and induction was done by fentanyl (1 µg/kg) and propofol (2 mg/kg) and atracurium (0.5 mg/kg) for endotracheal intubation. Mechanical ventilation was maintained with the endexpiratory carbon dioxide target from 34 to 36 mmHg using capnography. Inhalational anesthesia was used for maintenance of general anesthesia by isoflurane 1–2 vol. % in 100% O₂. Atracurium (0.1 mg/kg) was given every 30 min or when needed and 1 g paracetamol was given. After finishing the operation and before extubation, the block technique was performed. Paracetamol 1g was given every 8h postoperatively.

Technique of ultrasound-quided quadratus lumborum block

QLB was performed with the patient laying on the back and lateral tilt. After detecting the anterior superior iliac spine, the probe of ultrasound was placed on it and advanced cranially till identifying the muscles of abdominal wall. The external oblique muscle was followed till reaching its posterior border, and then a hook sign was visualized like a roof over the QLB muscle after leaving underneath the internal oblique muscle. The probe was angulated down to detect the middle layer of the thoracolumbar fascia that appeared as a shiny hyperechoic line, and then the needle was introduced in plane from anterolateral to posteromedial till its tip became between the QLB muscle and thoracolumbar fascia. The proper position of needle tip was confirmed after negative aspiration by injection of 5-ml of normal saline to the space with hypoechoic image. Bupivacaine 0.25% was used for ejection, and the volume injected was 0.2 ml/kg per side [10].

Technique of ultrasound-quided transversus abdominis plane block

TAP block was done while patients were in a supine position. At umbilical level in the anterior axillary line, the probe of ultrasound was placed between the lower costal margins cranially and the iliac crest caudally, and then the muscles of anterior abdominal wall were detected (external oblique, internal oblique, and transverse

abdominis muscles). Then, the needle was introduced in the plane between the internal oblique and transverse abdominis muscles. For avoidance of intravascular injection, negative aspiration was done before injection. Bupivacaine 0.25% was used for injection, and the volume injected was 0.2 ml/kg per side [7].

Data collection

- (1) The primary outcome was postoperative pain assessment using the VAS score.
- (2) The secondary outcomes were measurement of vital signs (SBP, DBP, MABP, and HR) at baseline before the operation and then after the operation on admission to PACU, after 30 min in PACU, and then at 2, 4, 8, 12, and 24h postoperatively; the total amount of rescue analgesia (pethidine); and the time to first analgesia request.

Statistical package and analysis

Analysis of the data was done by Statistical Package for the Social Sciences (SPSS, Armonk, NY: IBM Corp), version 22.0. Mean±SD was used for expression of quantitative data. Frequency and percentage were used for expression of qualitative data.

Tests used

- (1) Independent samples t test of significance was used for comparison of two means.
- (2) χ^2 test of significance was used for comparison of proportions between two qualitative parameters.
- (3) Mann-Whitney U test was used for nonparametric data comparison between the groups.
- (4) The margin of error accepted was set to 5%, with a confidence interval of 95%. As a result, the significance of the P value was determined as follows.

P value:

- (1) P value of less than 0.05 was considered significant.
- (2) P value of less than 0.001 was deemed highly significant.
- (3) Pvalue of more than 0.05 was declared nonsignificant.

A total of 46 patients participated in the study: 23 patients in QLB group and 23 patients in TAP block group.

Results

Demographics

Regarding demographic data, there was no statistically significant difference between groups, with P value more than 0.05 (Table 1).

Table 1 Comparison between groups regarding demographic

Demographic data	QLB group (n=23)	TAP group (n=23)	t/Z	<i>P</i> value
Age (years)	33.87 ± 7.1	36.5±9.6	1.1 ^t	0.29
Weight (kg)	83.3 ± 6.9	83.1 ± 7.7	0.1 ^t	0.92
Height (cm)	172.65 ± 6	173.4 ± 7.2	0.4	0.69
Duration of surgery (min)	147.4 ± 47.4	143.5±49.3	0.27 ^t	0.79
ASA	1 (1–2)	1 (1–2)	0.2 ^z	0.77

Data were represented as mean±SD, median (interquartile range). ASA, American Society of Anesthesiology; QLB, quadratus lumborum block; t, Student t test; TAP, transversus abdominis plane block; Z, Mann-Whitney test. P value more than 0.05 was not statistically significant.

Pain control

Regarding VAS score for pain assessment, there were statistical differences between the groups from PACU till 24h postoperatively, with P value less than 0.001 (Table 2).

Baseline vital data results

Regarding baseline vital data, there were no statistical differences between the groups, with P value more than 0.05 (Table 3).

Postoperative vital data results

Regarding postoperative vital data, there were statistical differences between the groups from PACU till 24h postoperatively, with P value less than 0.001 (Table 4).

According to DABP from PACU till 24h after surgery, there was a statistically significant difference between the QLB group and the TAP block group, with P value less than 0.001 (Table 5).

According to MABP from PACU till 24h after surgery, there was a statistically significant difference between QLB group and the TAP block group, with P value less than 0.001 (Table 6).

According to HR from PACU till 24h after surgery, there was a statistically significant difference between the QLB group and the TAP block group, with P value less than 0.001 (Table 7).

The time to first pethidine request was significantly longer in the QLB group than in the TAP group, with a significant difference (P<0.001) (Table 8).

Regarding the total dose of analgesic used in each group, postoperative pethidine consumption was more in the TAP group than the QLB group, with a significant difference (P<0.001) (Table 9).

Table 2 Comparison between groups regarding visual analog scale

Visual analog score Q	QLB group (n=23)	TAP group (n=23)	Mann-Whitney test	
			Z	P value
PACU admission	1 (1–2)	3 (2–3)	4.7	<0.001
30 min in PACU	1 (1–2)	3 (3–3)	5	< 0.001
2 h	2 (1–3)	3 (3–6)	4.1	< 0.001
4 h	2 (2–3)	5 (5–6)	5.2	< 0.001
8 h	3 (2–3)	5 (4–6)	4.4	< 0.001
12 h	3 (2–4)	5 (4.25–6)	4.2	< 0.001
24 h	2 (2-3)	5 (4–5)	5.3	< 0.001

Data were represented as median (interquartile range). PACU, postanesthetic care unit; QLB, quadratus lumborum block; TAP, transversus abdominis plane block. *P* value less than 0.05 was statistically significant.

Table 3 Comparison between groups regarding baseline vital data

	QLB group (n=23)	TAP group (n=23)	t	<i>P</i> value
SABP (mmHg)	125.8±5.97	126.3±5	0.32	0.75
DABP (mmHg)	76.5 ± 5.8	74.5 ± 5	1.27	0.21
MABP (mmHg)	92.8 ± 5.4	91.4 ± 4.1	0.98	0.33
HR (bpm)	80.2 ± 4.5	80.1 ± 3.8	0.1	0.92

Data were represented as mean±SD. bpm, beats per minute; DAPB, diastolic arterial blood pressure; HR, heart rate; MABP, mean arterial blood pressure; QLB, quadratus lumborum block; SAPB, systolic arterial blood pressure; t, Student t test; TAP, transversus abdominis plane block. P value more than 0.05 was not statistically significant.

Table 4 Comparison between groups regarding mean arterial blood pressure

	QLB group (n=23)	TAP group (n=23)	t	P value
SABP PACU (mmHg)	102.65±3.2	135.4±6.2	22.5	<0.001
SABP 30 min in PACU (mmHg)	103.2±2.9	136±6.1	23.3	<0.001
SABP 2h (mmHg)	109.1 ± 3.2	137.3 ± 4.5	24.5	< 0.001
SABP 4h (mmHg)	112.8 ± 3.3	137.6 ± 4.4	21.7	< 0.001
SABP 8h (mmHg)	117.4 ± 2.5	136.5 ± 3.8	20.2	< 0.001
SABP 12h (mmHg)	120.96 ± 2.7	136.3 ± 3.7	15.8	< 0.001
SABP 24h (mmHg)	121.9±3.6	134.5±4.2	10.9	<0.001

Data were represented as mean \pm SD. PACU, postanesthetic care unit; QLB, quadratus lumborum block; SAPB, systolic arterial blood pressure; t, Student t test; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

Discussion

The result of the study revealed that the QLB is more effective in pain control than TAP block following paraumbilical hernia repair. The results of VAS score and postoperative vital data (SPB, DBP, MABP, and HR) from PACU till 24h postoperatively were lower in the QLB group than the TAP group. The total amount of pethidine was lower in the QLB group, and the time to first rescue analgesia request was longer in the QLB group.

The difference between the QLB and TAP groups was not statistically significant regarding age, weight, height, duration of surgery, and ASA. This is in line

Table 5 Comparison between groups regarding diastolic arterial blood pressure

	QLB group (n=23)	TAP group (n=23)	t P value
DABP PACU admission (mmHg)	61.9±4.6	88.4±4.1	20.5 <0.001
DABP 30 min in PACU (mmHg)	63.7 ± 3.98	88.78±3.1	23.86 < 0.001
DABP 2h (mmHg)	68.3 ± 3.66	90 ± 3.3	21.29 < 0.001
DABP 4h (mmHg)	70.7 ± 3.4	91 ± 3.6	19.59 < 0.001
DABP 8h (mmHg)	73.6 ± 3.1	90.1 ± 2.9	18.9 < 0.001
DABP 12h (mmHg)	77.3 ± 2.7	90.2 ± 2.7	15.98 < 0.001
DABP 24h (mmHg)	76.3 ± 5	89.1 ± 2.6	10.7 < 0.001

Data were represented as mean±SD. DAPB, diastolic arterial blood pressure; PACU, postanesthetic care unit; QLB, quadratus lumborum block; t, Student t test; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

Table 6 Comparison between groups regarding mean blood pressure

	QLB group (n=23)	TAP group (n=23)	t	P value
MABP PACU admission (mmHg)	75.5±3.7	104.1 ± 4.6	23.3	<0.001
MABP 30 min in PACU (mmHg)	76.8±3.1	104.4±3.9	26.9	<0.001
MABP 2h (mmHg)	81.9 ± 2.97	105.9 ± 3.6	24.6	< 0.001
MABP 4h (mmHg)	84.6 ± 2.8	106.6 ± 3.67	22.9	< 0.001
MABP 8h (mmHg)	88.1 ± 2.4	105.5 ± 3.1	21.2	< 0.001
MABP 12h (mmHg)	91.87 ± 2.8	105.7 ± 2.8	16.7	< 0.001
MABP 24h (mmHg)	91.65 ± 3.97	104.26 ± 2.7	12.56	<0.001

Data were represented as mean±SD. MABP, mean arterial blood pressure; PACU, postanesthetic care unit; QLB, quadratus lumborum block; t, Student t test; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

with the study by Öksüz *et al.* [11], which compared the QLB and TAP block for pain relief following lower abdominal surgery in children. The study included 53 patients, and the results showed there were no significant differences between the groups according to age, sex, weight, ASA score, operation type, or operating time.

Kumar and colleagues performed a prospective doubleblinded study on 70 patients comparing TAP block versus QLB for postoperative analgesia following

Table 7 Comparison between groups regarding heart rate

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	QLB group (n=23)	TAP group (n=23)	t	<i>P</i> value
HR PACU admission (bpm)	71.4 ± 4.4	92.3±5.97	13.6	<0.001
HR 30 min in PACU (bpm)	74.1 ± 4.1	95.3±5.8	14.3	<0.001
HR 2h (bpm)	76.78 ± 5	100 ± 8.7	11.1	< 0.001
HR 4h (bpm)	79.3 ± 4.75	103.7 ± 7.98	12.6	< 0.001
HR 8h (bpm)	83.26 ± 5.3	101.9 ± 8	9.3	< 0.001
HR 12h (bpm)	84.3 ± 6.35	99.65 ± 6.1	8.3	< 0.001
HR 24h (bpm)	81.7 ± 4.7	92.4 ± 4.3	8	< 0.001

Data were represented as mean±SD. bpm, beats per minute; HR, heart rate; PACU, postanesthetic care unit; QLB, quadratus lumborum block; t, Student t test; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

Table 8 Comparison between groups regarding time to first pethidine request

QLB group (n=23)	TAP group (n=23)	t test	P value
554.3±200.7	201.8 ± 171.3	6.18	<0.001
	(n=23)	(n=23) (n=23)	0 1

Data were represented as mean±SD. QLB, quadratus lumborum block; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

Table 9 Comparison between groups regarding total dose of pethidine within 24h as a rescue analgesia

	QLB group (n=23)	TAP group (n=23)	t test	<i>P</i> value
Postoperative pethidine consumption (mg)	86.96±50.49	247.8±94.7	7.19	<0.001

Data were represented as mean±SD. QLB, quadratus lumborum block; TAP, transversus abdominis plane block. P value less than 0.05 was statistically significant.

lower abdominal surgeries and showed no significant differences between the groups regarding age, sex, BMI, and surgery time, which matched with our results [9].

Our study's primary outcome was to compare pain control postoperative between the two groups. VAS was the score used for pain assessment postoperatively and used at regular periods (at PACU admission, 30 min in PACU, 2, 4, 8, 12, and 24 h), from PACU till 24h postoperative, and our results showed that the QLB was more efficient in pain control than the TAP block, with P value less than 0.001. The overall VAS score in the QLB group was lower than the TAP block group. Huang et al. [12] in a RCT study that include 80 patients showed that there were significant differences between the groups regarding VAS score for pain assessment postoperatively during movement and at rest (P<0.006), which is in line with our results.

The study by Öksüz and colleagues showed that there were significant differences observed between the groups regarding pain control. The postoperative 30min and 1-,2-, 4-, 6-, 12-, and 24-h FLACC scale (face, leg, activity, cry, and consolability) results were lower in the QLB group compared with the TAP block group (P<0.05). The QLB group had greater parent satisfaction scores than the TAP block group (P < 0.05), and this agreed with our results [11].

The results of a prospective double-blinded study done by Kumar and colleagues on comparing the pain scores between the two groups based on the numeric pain intensity scale at rest for various time periods showed a significant difference at the 1, 2, 4, 6, and 8 h postoperatively, with P value less than 0.001, at 10 h, with P value of 0.002, at 12 h, with P value of 0.015, and at 16 h postoperatively, with P value of 0.022, and these results are in line with our study results [9].

A randomized-controlled trial performed by Verma and colleagues included 60 patients for comparing QLB versus TAP block after cesarean section analgesia and showed that the VAS was significantly lower in the QLB group than in the TAP group, taking into account VAS at rest and with movement at all time points after cesarean section (2, 4, 6, 12, 24, 36, 48, and 72 h), which is agreement with our results [13].

El-Boghdadly and colleagues compared QLB versus TAP block in a systematic review and network metaanalysis, and their results without neuraxial morphine, QLB, and/or TAP block were found to be more effective in lowering pain scores at rest as well as pain scores on movement (4-6, 8-12, 24, 36, and 48 h), and this is matched with our study [14].

Postoperative vital data in the form of noninvasive arterial blood pressure (SBP, DBP, and MABP) and HR were one of our study's secondary outcomes, and there were statistical differences between the groups from PACU till 24h postoperatively, with P value less than 0.001. The vital data in the QLB group were lower than the TAP group. This agreed with the study by Saleh and colleagues, who compered QLB (transmuscular approach) versus TAP block (unilateral subcostal approach) for perioperative analgesia after open nephrectomy and included 48 patients. The results of the intraoperatively obtained mean arterial pressure revealed substantial disparities between the groups. The intraoperative HR between the groups likewise showed statistically significant differences. During the 12-h postoperative period, the average HR and mean arterial pressure measures revealed substantial variations between the groups [15].

Regarding the total amount of rescue analgesia (pethidine) in milligram that was given intravenously from PACU till 24h postoperatively and the time to first rescue analgesia request, the results were significantly different between the two groups. The QLB group consumed lower amounts of pethidine than the TAP group, and the time to first analgesia request was longer in the QLB group, with P value less than 0.001. This matched with the results of Huang and colleagues. The OLB group used much less PCA morphine 24h after surgery than the TAP group, according to the findings, with P value less than 0.001. The first PCA morphine demand was the sixth postoperative hour for the TAP group and 12th hour for the QLB group [12].

The results of the study by Öksüz et al. [11] showed that lower number of patients needed analgesia in the first day postoperatively in the QLB group in comparison with the TAP block group, with P value less than 0.05, and this matched with our study.

A study by Kumar and colleagues demonstrated that in the QLB group, the time passed before the need for first supplemental analgesia was much longer than in the TAP block group and the total morphine consumption was lesser in QLB group compared with the TAP group, with P value less than 0.001, and this matched with our results [9].

The primary outcome of the trial by Verma and colleagues corroborated our findings, showing that in the QLB group, the time for rescue analgesic necessity (injection tramadol 100 mg intravenously) was substantially longer than in the group TAP (*P*=0.001). In comparison with the TAP group, the need for analgesics was dramatically reduced in the QLB group after 72 h. Only 13 patients in the QLB group needed a single dosage of analgesia, and 17 patients did not, but patients nos. 1, 19, and 10 in the TAP group required 6, 7, and 8 doses of analgesia, respectively, which was statistically significant (P=0.000), and this is similar to our results [13]. Blanco and colleagues conducted a study in 2016 that included 76 patients and compared QLB to TAP block for pain control following cesarean section. Patients who received QLB had significantly lower cumulative morphine doses than those who received TAP block, after 6h (P=0.040), 12h (P=0.025), 24h (P=0.006), and 48h (P=0.014) after cesarean delivery (P=0.005). At rest and with activity, the areas under the curve for total pain reduction were similar (P=0.001), which is in line with our study [7].

Conclusion

The study concluded that OLB is more effective for pain control following paraumbilical hernia repair than TAP block and requires less amount of opioids postoperatively as a rescue analgesia.

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Conflicts of interest

There are no conflicts of interest.

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