

Comparison between Ultrasound Guided Erector Spinae Plane Block and Quadratus Lumborum Block for Postoperative Pain Management in Patient Undergoing Open Nephrectomy

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Abstract:

Background: Nephrectomy is conducted to manage renal malignancies and for purpose of living donor kidney transplantation. This study aims to compare analgesic effectiveness of ESPB versus QLB type III in open nephrectomy surgeries. **Methods:** This randomized, double-blind trial was carried out on a cohort of 75 cases underwent open nephrectomy surgeries. Patients were distributed into three evenly matched groups: Group I: received only general anesthesia (GA), group II: received ESPB and group III: received QLB type III. **Results:** Time of first rescue analgesia and recovery time were notably delayed in ESPB group and QLB group than controls ($P < 0.001$). Both ESPB and QLB required a significantly reduced total morphine dose within first 24 hours relative to controls ($P < 0.001$). VAS at rest and deep breath and coughing were significantly lower at 1h, 2h, 4h, 6h, 8h, and 12 h in ESPB group and QLB group than controls ($P < 0.05$). Compared to controls, ESPB and QLB groups exhibited significantly lower incidences of postoperative nausea, vomiting, urinary retention, itching, and shorter hospitalization durations ($P < 0.05$). Additionally, patient satisfaction levels were notably elevated in ESPB and QLB groups relative to controls ($P < 0.05$). **Conclusions:** ESPB and QLB type III were both effective in management of pain and maintaining hemodynamic stability, as well as, delaying time to first rescue and reducing opioid consumption in patients underwent open nephrectomy surgeries.

Keywords: Erector Spinae Plane, Ultrasound, Quadratus Lumborum, Pain Management, Open Nephrectomy.

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Introduction

Nephrectomy is conducted to address renal malignancies and for purpose of living donor kidney transplantation⁽¹⁾. Although laparoscopic procedures are becoming more widespread, open surgery continues to be a frequently utilized approach for patients needing partial or radical nephrectomy. In subsequent months after surgical intervention, this method is closely associated with a significant occurrence of intense postoperative pain and subsequent emergence of long-term chronic pain⁽²⁾. Pathogenesis of acute pain is elucidated as a result of reflexive muscle spasm, spinal cord pain pathways activation, and inflammatory cell infiltration⁽³⁾. Utilizing a multimodal analgesic regimen that combines multiple pain management techniques with local or regional anesthesia is essential to enhance its overall efficacy⁽⁴⁾. Owing to their ability to reduce reliance on intravenous analgesics and enhance patient-reported satisfaction, regional anesthesia approaches are often advocated as preferred method for pain control in context of open nephrectomy procedures⁽⁵⁾.

ESPB was initially described by Forero et al.⁽⁶⁾ as an analgesic approach for managing thoracic neuropathic pain. This innovative fascial block technique enables sensory blockade across multiple abdominal and thoracic wall segments. Moreover, ESPB has been widely applied in both pediatric and adult populations for various clinical purposes, including thoracic and breast procedures (T4-5), chronic shoulder pain (T2), and upper abdominal surgeries (T7-8)⁽⁷⁾. In ESPB, a local anesthetic (LA) is administered into deep fascial plane of ESM at vertebral transverse process. This deposited LA diffuses into epidural, paravertebral, and intercostal spaces, exerting its anesthetic effect on these regions⁽⁸⁾.

The QLB represents another commonly employed regional anesthesia approach. It has been applied to alleviate postoperative

pain in a range of surgeries, such as laparotomies, hip surgeries, minimally invasive laparoscopic procedures, and cesarean deliveries⁽⁹⁾. Initially described by Blanco in 2007, this technique involved injection of local anesthetic into anterolateral aspect of quadratus lumborum muscle, later identified as type I QLB while type III QLB involves injection of local anesthetic at interface between quadratus lumborum and psoas major muscles traversing quadratus lumborum muscle⁽¹⁰⁾.

Adequate postoperative pain control is essential to avoid unnecessary patient discomfort and can aid in reducing morbidity, shortening hospital stays, and lowering healthcare costs. On other hand, inadequate postoperative analgesia can result in adverse physiological and psychological outcomes, elevating morbidity and mortality, which in turn prolongs recovery and delays patient's return to normal life activities⁽¹¹⁾.

The goal of this work is to compare analgesic effectiveness of low thoracic ESPB versus QLB type III in open nephrectomy surgeries.

Patients and Methods:

This randomized, double-blind, prospective controlled study was performed on a cohort of 75 patients aged between 20 and 60 years, both sexes, ASA I and II scheduled for open nephrectomy surgeries under GA at Benha University Hospital. With authorization granted by Ethical Committee of Benha University Hospitals in Benha, Egypt, research was carried out from August 2022 to June 2024. Prior to enrollment in study, all participants were granted informed written consent.

Exclusion criteria encompassed individuals with ASA physical status III or IV, those undergoing chronic analgesic therapy, a history of opioid dependency, hypersensitivity to local anesthetics or opioids, morbid obesity accompanied by comorbid conditions, psychiatric patients

unable to effectively communicate with investigators, individuals with skin infections at puncture site, and patients with bleeding or coagulation abnormalities.

Randomization and blindness:

A web-based randomization platform was utilized to produce a randomized numerical sequence (<http://www.randomizer.org>) was used for random allocation and each patients' code was kept in an opaque sealed envelope. Patients were randomly allocated with 1:1:1 allocation ratio into three equal groups in a parallel manner: Group I: received only GA as control group, group II: received ESPb and group III: received QLB type III. Outcome assessors and also cases were blinded.

Methods:

All cases underwent comprehensive history taking, thorough clinical examination, and laboratory assessments, as well as liver and kidney function tests.

On day preceding surgery, all patients were thoroughly briefed on method of postoperative pain evaluation utilizing VAS score. VAS ranges from 0, indicating "no pain," to 10, representing "the most unbearable pain conceivable."⁽¹²⁾

Intraoperatively, patient was positioned in a semi-sitting posture, inclined at an angle of 30 to 45 degrees. Pulse oximetry, ECG, non-invasive blood pressure monitoring, temperature probe and capnography was utilized for standard monitoring of patients. Venous access was established. A light premedication consisting of midazolam at a dosage of 0.01-0.02 mg/kg was administered to patient. Oxygen supplementation at 2-3 L/min was delivered via nasal cannula to prevent hypoxemia following premedication. Additionally, a pulse oximeter and non-invasive blood pressure cuff were applied for continuous monitoring. All groups were administered general anesthesia using propofol at 2 mg/kg, atracurium at 0.5 mg/kg, and fentanyl at 2 µg/kg for induction.

Anesthesia was sustained with 1.2% isoflurane in a 50% air-oxygen mixture. Atracurium was administered at a dose of 0.1 mg/kg every 20 minutes to ensure continuous muscle relaxation throughout surgical procedure. End-tidal carbon dioxide levels were stabilized around 35 mmHg by intubating all patients and managing their ventilation through volume-controlled positive pressure mechanical ventilation, with a tidal volume of 6-8 ml/kg and an inspiratory-to-expiratory ratio of 1:2. Group (II, III) technique was done after receiving general anesthesia using (low or high) frequency probe of (LOGIQ™e) ultrasonography and A 22-gauge, 80 mm needle (Stimuplex D, B-Braun, Germany).

Group II (The ultra-sound guided ESPb):

The patient was placed in lateral decubitus position, depending on specific surgical site chosen. After aseptic preparation and draping of upper back skin, seventh thoracic vertebra (T7) was located by counting downward from spine of seventh cervical vertebra (C7). This process corresponded to apex of scapular spine. To locate transverse process of T7, a high-frequency LOGIQ™e ultrasound probe was placed transversely over T7 vertebral spine and gradually shifted laterally. Subsequently, probe was adjusted into a sagittal orientation, allowing clear visualization of erector spinae muscles located underneath trapezius. Using an in-plane ultrasound-guided technique, a 22-gauge, 80-mm needle was advanced medially towards transverse process. To verify precise needle placement beneath anterior fascia of erector spinae, 1 ml of normal saline was injected. Upon confirmation, 30 ml of 0.25% bupivacaine was administered into compartment created below erector spinae muscle.

Group III (The ultra-sound guided QLB type III):

Based on surgical site, patient was positioned in lateral decubitus posture. Following antiseptic preparation and

appropriate skin draping, probe was aligned horizontally along anterior axillary line, at midpoint between subcostal margin and iliac crest, facilitating identification of three abdominal muscle layers. This was accomplished using a low-frequency convex LOGIQTMe ultrasound probe. probe was then shifted to posterior axillary line to visualize quadratus lumborum muscle, clearly showing its attachment to lateral border of L4 vertebral transverse process. Psoas major muscle appeared anteriorly, erector spinae muscle posteriorly, while quadratus lumborum muscle was seen affixed to apex of transverse process. A distinct shamrock-like configuration emerged, characterized by three "leaves" representing anatomical structures. An 80-mm, 22-gauge needle was advanced in-plane under ultrasound guidance, from a posterior-to-anterior direction, traversing quadratus lumborum muscle to reach interface between quadratus lumborum and psoas major muscles. Needle tip placement was confirmed through hydro-dissection with 1 ml of normal saline following negative blood aspiration. Subsequently, 30 ml of 0.25% bupivacaine was administered. Regardless of group assignment, all patients received intravenous acetaminophen (15 mg/kg) and ketorolac (0.5 mg/kg) 30 minutes before surgery completion to manage postoperative pain. Following muscle relaxant reversal using neostigmine at 0.04–0.07 mg/kg and atropine at 0.02 mg/kg, patients were gradually awakened from anesthesia, extubated, and transitioned to an oxygen–air mixture in PACU. Postoperative pain management continued in ward with a standardized regimen of acetaminophen (15 mg/kg per dose, administered four times daily for 2 days) and ketorolac (0.5 mg/kg per dose, given three times daily for 2 days). All patients received regular Paracetamol (inject Amol, pharco B International, Phama Tech) 1 gm/6 hours. Rescue analgesia was provided via an IV bolus of morphine at a dose of 0.05 mg/kg

when postoperative VAS score was ≥ 4 or upon patient request for additional pain relief between VAS assessments. This dose was titrated up to 1 mg every 60 minutes, as required, to maintain VAS scores below 3.

Adverse effects were assessed, including hypotension (defined as a 20% reduction from baseline mean arterial pressure), bradycardia (a 20% drop-in baseline heart rate), and respiratory depression (SpO₂ falling below 95% and necessitating supplemental oxygen). IV boluses of ondansetron at a dosage of 0.1 mg/kg were administered to alleviate PONV.

Total morphine consumption in first 24h, All patients were provided with intravenous morphine (0.05 mg/kg) then titration of 1mg/60 min as required to keep VAS scores less than 3 and morphine consumption after 24hours was recorded. A block was deemed failed if patient required more than two doses of rescue analgesia within first postoperative hour, as indicated by block failure rate. Patient satisfaction with block's effectiveness and postoperative pain relief was gauged using an 11-point satisfaction scale (0 = not satisfied, 10 = highly satisfied). scale was further divided into three categories: 0-3 (dissatisfied), 4-6 (moderate), and 7-10 (satisfied)⁽¹³⁾.

The primary outcome was VAS was measured. Secondary outcomes encompassed assessment of hemodynamic variables and total amount of morphine consumed during initial 24 hours following surgery, post-operative pain reliever, complications failure rate of block, patients' satisfaction related to block performance, incidence of complications and duration of hospital stays from first day postoperative until discharge.

Sample Size Calculation:

Using OpenEpi program, calculated sample size amounted to 75 cases, distributed equally into three groups with 25 cases per group. This calculation was based on a 95% confidence level, 80%

power, and accounting for a 10% non-response rate. It was anticipated that cumulative morphine consumption in the controls would be 4 ± 1.7 mg, while in QLB group it would be 3 ± 1.3 mg, expressed as mean \pm standard deviation (14).

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Statistical analysis

SPSS version 27 (IBM©, Chicago, IL, USA) was employed to conduct statistical analyses. Shapiro-Wilk test and visual examination of histograms were employed to assess normality of data. ANOVA (F) test was employed to analyze parametric data, which was represented as mean \pm standard deviation (SD). Additional comparisons were made using Tukey's post hoc test. Categorical variables, which were presented as frequencies and percentages (%), were assessed using Chi-square test. Kruskal-Wallis test and Mann-Whitney U test were employed to conduct group comparisons, and non-parametric quantitative data were expressed as median and interquartile range (IQR). Threshold for statistical significance was established as a two-tailed P value below 0.05.

Results:

A total of seven patients chose not to participate, and fourteen were deemed ineligible based on inclusion criteria. Out of 96 patients screened for eligibility, 75 were randomly allocated into three equal groups. All assigned patients were included in statistical analysis and monitored throughout follow-up period. Figure 1

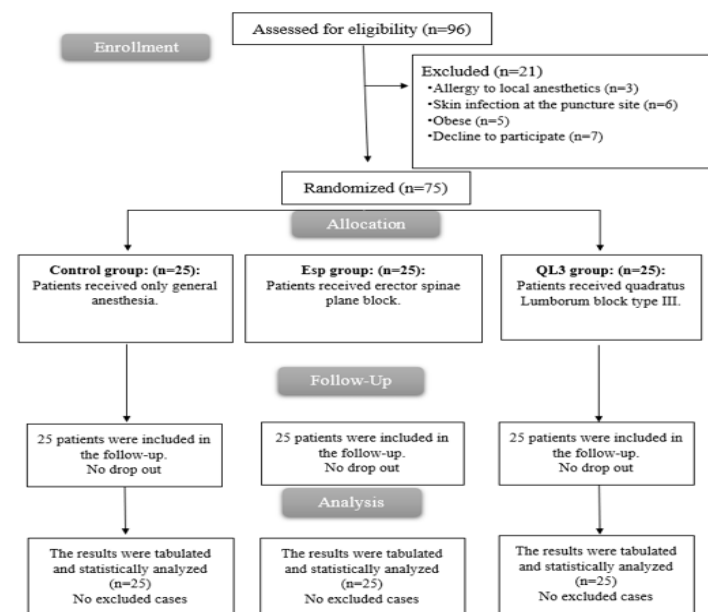
No significant differences were detected among three groups with respect to sex, age, height, weight, ASA physical status, BMI, or surgery duration. Table 1

VAS at rest and deep breath and coughing were insignificantly different at PACU, 30 min and 24 h among three groups and were significantly different at 1h, 2 h, 4h, 6h, 8h and 12h among three groups (P<0.05). At 1, 2, 4, 6, 8, and 12 hours, VAS scores for rest, deep inhalation, and coughing were notably lower in both ESPB and QLB groups compared to controls (P < 0.05). However, no significant variation was observed between ESPB and QLB groups. Table 2

Table 1: Demographic data and duration of surgery of studied groups

		Control group (n=25)	ESPB group (n=25)	QLB group (n=25)	P
Age (years)		43.1 \pm 10.05	44.5 \pm 12.83	42.7 \pm 12.39	0.859
Sex	Male	11 (44%)	13 (52%)	14 (56%)	0.688
	Female	14 (56%)	12 (48%)	11 (44%)	
Weight (kg)		74.8 \pm 11.5	78.2 \pm 11.08	74.7 \pm 11.58	0.475
Height (m)		1.66 \pm 0.06	1.67 \pm 0.07	1.68 \pm 0.06	0.698
BMI (kg/m ²)		27.2 \pm 4.55	27.9 \pm 2.91	26.6 \pm 3.93	0.501
ASA physical status	I	14 (56%)	17 (68%)	15 (60%)	0.675
	II	11 (44%)	8 (32%)	10 (40%)	
Duration of surgery (min)		151.4 \pm 20.69	155.2 \pm 15.31	150.2 \pm 18.17	0.600

Data are presented as mean \pm SD or frequency (%). ESPB: erector spinae plane block, QLB: quadratus lumborum block, BMI: Body mass index, ASA: American society of anesthesiologists.



ESP: erector spinae plane block, QL3: quadratus lumborum block type III.

Figure 1: CONSORT flow chart of enrolled patients.

Table 2: VAS at rest and VAS at deep breath and coughing of studied groups

VAS at rest	Control group (n=25)	ESPB group (n=25)	QLB group (n=25)	P
At PACU	0(0 - 1)	0(0 - 1)	0(0 - 1)	0.761
30 min	1(1 - 1)	1(1 - 1)	1(0 - 1)	0.893
1h	3(2 - 3)	1(1 - 2)	1(1 - 2)	<0.001*
2h	4(3 - 5)	1(1 - 3)	1(1 - 2)	<0.001*
4h	3(3 - 5)	1(1 - 2)	1(1 - 2)	<0.001*
6h	4(3 - 5)	4(1 - 4)	3(1 - 4)	0.01*
8h	4(3 - 5)	3(2 - 4)	3(2 - 4)	0.007*
12h	4(4 - 5)	4(3 - 5)	4(4 - 4)	0.016*
24h	4(4 - 6)	4(4 - 5)	4(3 - 4)	0.836
VAS at deep breath and coughing				
At PACU	1(0 - 1)	1(1 - 2)	1(0 - 2)	0.366
30 min	2(1 - 2)	2(1 - 2)	2(1 - 3)	0.544
1h	2(2 - 3)	2(1 - 2)	1(1 - 2)	0.001*
2h	4(2 - 6)	2(1 - 3)	2(1 - 3)	<0.001*
4h	5(3 - 5)	2(1 - 3)	2(1 - 3)	<0.001*
6h	5(4 - 6)	4(1 - 4)	3(3 - 4)	0.003*
8h	5(4 - 7)	4(3 - 5)	4(3 - 5)	0.009*
12h	5(5 - 8)	4(4 - 5)	4(3 - 5)	0.003*
24h	6(4 - 7)	6(5 - 7)	5(5 - 6)	0.361

Data are presented as median (IQR). *: significant as P value ≤ 0.05. P1: P value between Control group and ESPB group, P2: P value between Control group and QLB group, P3: P value between ESPB group and QLB group, ESPB: erector spinae plane block, QLB: quadratus lumborum block, VAS: Visual analog scale.

Postoperative HR and MAP were insignificantly different at PACU, 15min, 30 min, 17h, 19h, 21h and 23 h among three groups and were significantly different at 1h, 3 h, 5h, 7h, 9h, 11h, 13h and 15h among three groups (P <0.05). Postoperative HR and MAP were significantly lower at 1h, 3h, 5h, 7h, 9h, and 11h, 13h and 15h in ESPB group and QLB group than controls (P<0.05) and were not significantly different between ESPB and QLB groups. Figure 2, Figure 3 Significant variations were observed among three groups concerning time to first rescue analgesia, cumulative morphine dosage administered in first 24 hours, and recovery duration (P<0.001). Time of first rescue analgesia and recovery time were significantly delayed in ESPB group and QLB group than controls (P<0.001) and was insignificantly different

between ESPB group and QLB group. Cumulative morphine consumption over initial 24-hour period was notably lower in both ESPB and QLB groups compared to controls (P < 0.001). However, no significant variation was identified between ESPB and QLB groups. Table 3 PONV, urine retention and itching were significantly lower in ESPB group and QLB group than controls (P<0.05). Nerve injury, hematoma, LA toxicity and intra vascular injection and failure rate didn't occur in any patient in three groups. Patient satisfaction was markedly higher in ESPB and QLB groups compared to controls (P <0.001). Additionally, hospital stays were considerably shorter in both ESPB and QLB groups compared to controls (P <0.05), with no significant variation observed between ESPB and QLB groups. Table 4

Table 3: Time of first rescue analgesia and total dose of morphine during first 24 hours of studied groups

	Control group (n=25)	ESPB group (n=25)	QLB group (n=25)	P
Time of first rescue analgesia (h)	2.8 ± 0.93	6.7 ± 0.9	7.1±0.95	<0.001*
	P1<0.001*, P2<0.001*, P3=0.285			
Total dose of morphine during first 24 hours (mg)	14 ± 2.94	9.7 ± 2.53	9.2 ± 2.53	<0.001*
	P1<0.001*, P2<0.001*, P3=0.771			

Data are presented as mean ± SD. * Significant as P value ≤ 0.05. P1: P value between Control group and ESPB group, P2: P value between Control group and QLB group, P3: P value between ESPB group and QLB group, ESPB: erector spinae plane block , QLB: quadratus lumborum block.

Table 4: Complications, patient satisfaction, hospital stays and failure rate of studied groups.

	Control group (n=25)	ESPB group (n=25)	QLB group (n=25)	P
PONV	10 (40%)	4 (16%)	3 (12%)	0.038*
Urine retention	8 (32%)	2 (8%)	1 (4%)	0.01*
Itching	5 (20%)	1 (4%)	0 (0%)	0.022*
Nerve injury	0 (0%)	0 (0%)	0 (0%)	---
Hematoma	0 (0%)	0 (0%)	0 (0%)	---
LA toxicity	0 (0%)	0 (0%)	0 (0%)	---
Intra vascular injection	0 (0%)	0 (0%)	0 (0%)	---
Satisfied	3 (12%)	18 (72%)	20 (80%)	
Good	2 (8%)	4 (16%)	3 (12%)	
Fair	16 (64%)	2 (8%)	2 (8%)	< 0.001*
Unsatisfactory	4 (16%)	1 (4%)	0 (0%)	
Hospital stays (days)	5.5 ± 1.19	4.7 ± 0.89	4.4 ± 0.65	0.001*
	P1=0.015*, P2<0.001*, P3=0.545			
Failure rate	--	0 (0%)	0 (0%)	--

Data are presented as mean ± SD or frequency (%). * Significant as P value ≤ 0.05. P1: P value between Control group and ESPB group, P2: P value between Control group and QLB group, P3: P value between ESPB group and QLB group, ESPB: erector spinae plane block, QLB: quadratus lumborum block POVN: postoperative nausea and vomiting, LA: local anesthetic.

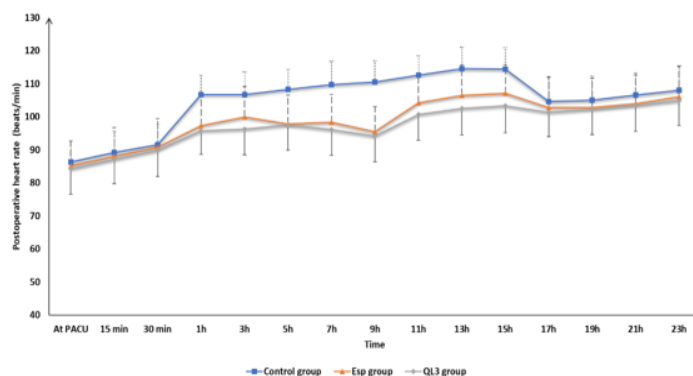


Figure 2: Postoperative heart rate of studied groups.

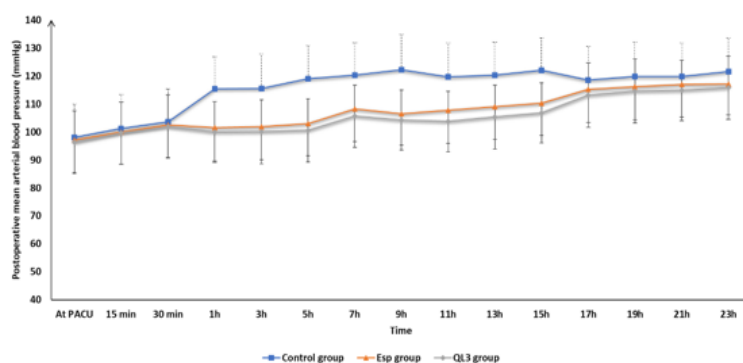


Figure 3: Postoperative means arterial blood pressure of studied groups

Discussion:

Patients requiring partial or radical nephrectomy frequently undergo open surgical procedures. In postoperative period, this approach is notably associated with development of severe acute pain and prolonged chronic pain in the following months⁽¹⁵⁾.

In present study, VAS at rest was significantly lower at 1h, 2h, 4h, 6h, 8h, and 12 h in ESPB group QLB group than controls and was insignificantly different between ESPB group and QLB group. VAS at deep breath and coughing was significantly lower at 1h, 2h, 4h, 6h, 8h and 12 h in ESPB and QLB groups than controls and was insignificantly different between ESPB and QLB groups. In agreement with our results, Hetta et al.⁽¹⁶⁾ reported that VAS at rest was notably lower in ESPB group and QLB group than controls with no significant variation between ESPB group and QLB group. However, VAS at dynamic was notably

lower in ESPB group, QLB group and controls. This difference may be attributed to different volume of anesthetic drug (20ml) and different sample size. ESPB group, as shown by Abdelaziz et al.,⁽¹⁷⁾ exhibited significantly lower VAS scores than QLB group during both rest and sneezing, which contrasts with our results. In agreement with our results about hemodynamic measurements, Abdelaziz et al.⁽¹⁷⁾ found that postoperative HR and MAP was insignificantly different between QLB group and ESPB group. In contrast with our results, Baran et al.⁽¹⁸⁾ who reported that postoperative heart rate was considerably higher in QLB group than those in controls and ESPB group; however, it did not differ significantly between ESPB and controls. In present study, time of first rescue analgesia and recovery time were significantly delayed in ESPB group and QLB group than controls and was insignificantly different between ESPB group and QLB group. Our findings

agreed with, Baran et al. ⁽¹⁸⁾ who illustrated that first rescue analgesic requirement time was notably higher in QLB and ESPB groups than in controls; also, it did not differ significantly between QLB and ESPB groups. In agreement with our results, Abdelgalil et al. ⁽¹⁹⁾ showed that time of first rescue was significantly in group ESPB longer than in controls. However, Fakhry et al. ⁽²⁰⁾ who illustrated that time for raising request first rescue analgesic was notably longer in ESPB group than in QLB group.

In our investigation, total morphine consumption during initial 24-hour period was markedly lower in ESPB and QLB groups compared to controls. However, no significant variation was observed between ESPB and QLB groups. Our finding is corroborated by, Baran et al. ⁽¹⁸⁾ who demonstrated that opioid consumption was considerably lower in QLB and ESPB groups than in controls. Furthermore, there was no significant difference between ESPB and QLB groups as well. Abdelgalil et al. ⁽¹⁹⁾ corroborated our findings in their study, showing that cumulative morphine consumption during initial 48 hours was notably reduced in ESPB group compared to controls. Similarly, Elkotory et al. ⁽²¹⁾ conducted that total dose of morphine was insignificantly different between ESPB group and QLB group. In contrast with our results, Fakhry et al. ⁽²⁰⁾ found that opioid consumption during first 24 hours was notably lower in ESPB group than QLB group.

In present study, PONV, urine retention and itching were considerably lower in ESPB group and QLB group than controls. Nerve injury, hematoma, LA toxicity and intra vascular injection didn't occur in any patient in three groups. In same line, Zhang et al. ⁽²²⁾ who conducted that PONV, urine retention, itching, nerve injury, hematoma, LA toxicity and intra Vascular were insignificantly different between ESPB group and QLB group. Similarly, Abdelaziz et al. ⁽¹⁷⁾ who found that PONV and cases of organ injury or

LA toxicity were insignificantly different between ESPB group and QLB group. This was in contrast with Fakhry et al. ⁽²⁰⁾ found that patient satisfaction was significantly better in ESPB group than QLB group.

In our research, hospital stay was markedly reduced in both QLB and ESPB groups compared to controls. However, difference between ESPB and QLB groups was not statistically significant. In same vein, Zhang et al. ⁽²²⁾ reported that duration of hospital stay following surgery was not substantially different between ESPB group and QLB group.

Limitations of study included that sample size was relatively small that may produce insignificant results. Study was in a single center. Not comparing ESPB and QLB in different types of surgery. Not comparing ESPB and QLB with different types of anesthetics, doses and concentrations.

Conclusions:

The ESPB and QLB type III were both effective in management of pain and maintaining hemodynamic stability, as well as, delaying time to first rescue and reducing opioid consumption in patients underwent open nephrectomy surgeries.

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Author contribution

The authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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