Original Article

Postoperative analgesic effect of adding neostigmine to levobupivacaine in ultrasound-guided spermatic cord block for testicular sperm extraction surgery

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Abstract

Background and Aims: Providing postoperative pain management in patients who underwent scrotal surgeries is achieved using several methods, one of which is the ultrasound-guided spermatic cord block (US-SCB). To enhance anesthesia quality and extend analgesia postoperatively, several agents have been added in conjunction with local agents. This study targeted assessing the results of combining neostigmine with levobupivacaine in US-SCB for providing perioperative analgesia in patients undergoing testicular sperm extraction (TESE) surgery.

Material and Methods: This double-blind, randomized controlled study was performed for 112 subjects undergoing TESE operation using general anesthesia. They were randomly and equally divided into two groups. All participants received bilateral US-SCB after induction of general anesthesia by 19 mL of levobupivacaine 0.5% combined with 1 mL of neostigmine 500 μg in (group N) or 1 mL of normal saline in (group C). The first analgesic dose request time and the amount of analgesic consumed in the first 24 h were the main points of comparison in both groups.

Results: The mean postoperative analgesia duration was noticeably increased in the N group compared to the C group, with a value of 480 ± 41.34 min versus 404 ± 34.14 min, independently ($P < 0.001$). Moreover, the total amount of postoperative analgesic consumption was remarkably decreased in group N when compared to group C without statistically remarkable divergence concerning complications between both groups.

Conclusion: Adding neostigmine to a local anesthetic solution in US-SCB proved to detain the first analgesic request postoperatively with reduced perioperative analgesia consumption, without significant side effects.

Keywords: Levobupivacaine, neostigmine, spermatic cord block, testicular sperm extraction surgery

Introduction

The testicular sperm extraction (TESE) procedure was first introduced in 1995 by Devroey *et al.*, by extracting the parenchyma of the testis aiming for living sperms.[1]

Anesthesia for these patients can be effectively achieved using several approaches, including local, spinal, and general anesthesia. Although using general anesthesia can be beneficial in controlling a patient's anxiety, it does not eliminate postoperative pain sensation, which can be solved by

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_14_24

How to cite this article: Wahdan AS, Moussa AA, Farag MA, Alayyaf HA, Mohamed MM. Postoperative analgesic effect of adding neostigmine to levobupivacaine in ultrasound-guided spermatic cord block for testicular sperm extraction surgery. J Anaesthesiol Clin Pharmacol 2025;41:333-9.

Submitted: 07-Jan-2024 **Revised:** 12-Mar-2024
Accepted: 12-Mar-2024 **Published:** 27-Jun-2024

a variety of oral analgesics, parenteral opioids, and neuraxial or regional analgesia techniques.[2]

One of the commonly used regional techniques for postoperative analgesia is the spermatic cord block (SCB), which was initially performed by blindly blocking the targeted nerves (ilioinguinal nerve, the sympathetic plexuses around the spermatic cord, and the genital branch of the genitofemoral nerve) but is presently done under ultrasonography guidance. It has proven to be of many benefits, including reliability, affordability, and suitability for intra-scrotal operations. Unfortunately, it does not provide skin coverage; thus, an extra step of local skin infiltration is essential to acquire optimum results.[3-5]

Consequently, adjuvants were added, including opioids, midazolam, epinephrine, dexamethasone, bicarbonate, clonidine, neostigmine, and tramadol, to prolong the block's postoperative duration as well as reduce the local anesthetic dose.[6]

Neostigmine is a parasympathomimetic agent that works as a reversible cholinesterase inhibitor. It is used to enhance muscle tones in myasthenia gravis patients and to reverse the effect of muscle relaxants in general anesthesia. Lately, it has proven to be a suitable adjunct to local agents by tethering to acetylcholinesterase enzyme, thus hindering acetylcholine breakdown and increasing the muscarinic receptors stimulation.[7,8]

Some clinical studies assessed the analgesic effects of peripherally given neostigmine intraarticularly,[9] intravenously,[10] and in supraclavicular brachial plexus.[11] All these studies showed that using neostigmine with the local anesthetic lengthens its duration without adverse effects. However, the evidence is still considered inadequate as other studies showed the lack of any beneficial analgesic results upon using neostigmine peripherally in addition to local agents, resulting in a controversial conflict.[12,13]

This study aimed to assess the effects of neostigmine when added to levobupivacaine in SCB to provide perioperative analgesia in patients undergoing the TESE procedure.

Material and Methods

This prospective randomized double-blinded study took place in the IVF center in the interim from September 2020 to November 2023 and involved 112 subjects of ASA class I or II, aged 18–60 years, having elective TESE surgery using general anesthesia, after acquiring the consent of the institutional research ethics committee (N-18-2020) and clinical trial registration (NCT04492319). An informed consent was signed by the subjects following an explanation of the study. Those refusing to participate, with ASA III/IV, morbidly obese (body mass index >40), having contra-indications to regional anesthesia and given pain medications within 24 h, or allergic to study agents were all excluded.

The process of dividing the subjects randomly into two equal groups of 56 patients each was achieved by a computer-generated number and concealed by sequentially numbered, sealed opaque envelopes. The injection fluid was prepared by the anesthesiologist's assistant, according to the closed envelope data. The same surgeon used a common surgical technique to perform all the surgical procedures. All the operating team members were blinded to the study solutions, and it was released only in emergencies. Each participant from different groups obtained a total equal volume of drugs via bilateral ultrasound guided SCB to prevent bias and alteration in local anesthetic concentration.

Group N: The participants received 19 mL of levobupivacaine 0.5% (Chirocaine®) plus neostigmine 500 μg (Epistigmin, Egyptian Int. Pharmaceutical Industries Co 0.5 mg/mL) in 1 mL of normal saline in a total volume of 20 mL.

Group C: The participants received 19 mL of levobupivacaine 0.5% (Chirocaine®) plus 1 mL of normal saline in a total volume of 20 mL.

One day before surgery, all subjects were assessed by taking a full comprehensive history, physical examination, and routine investigations. The aim of the study was explained to participants in full detail by both the surgeon and the anesthetist, including the visual analog scale (VAS) scores (with 0 indicating no pain to 10 indicating the worst pain).

On surgery day, after verifying a fasting duration of 6 h, the participants were brought into the operating theater, where a 20-G intravenous (IV) cannula was inserted and the patients were pre-medicated with IV ondansetron 75 μg/kg over 5 min. Monitors were connected, including pulse oximeter, five-lead electrocardiography, and non-invasive blood pressure. The baseline mean arterial blood pressure (MAP) and heart rate (HR) were documented pre induction, and then general anesthesia was achieved using intravenous propofol 2 mg/kg, cisatracurium 0.15 mg/kg, and fentanyl 0.5 μg/kg. Anesthesia was deepened using sealed face-mask ventilation with sevoflurane concentration equivalent to 2 MAC and 100% O2 with a total fresh gas flow of 3 l/min. When ventilation had reached a suitable depth and frequency and reflexes were sufficiently depressed, insertion of a reusable

laryngeal mask airway was done. Maintenance of anesthesia was done using sevoflurane with cisatracurium as a continuous infusion (1–2 mcg/kg/min). Then SCB was done in the supine position, following complete aseptic guidelines.

Technique of the block

Following groin sterilization, at the inguinoscrotal junction distal to the external ring of the inguinal canal, the palpation of the spermatic cord (SC) was done. The SC was then pulled gently to the surface and then a linear transducer of ultrasound (Sonoscape SSI6000, Sonoscape Company Ltd, Shenzen, China) was used to visualize a semi-circle formation containing vas deferent, which appeared as a round non-compressible structure with no Doppler flow, and the testicular artery was identified by Doppler US. Next, 2 mL of 1% lidocaine was used to infiltrate the skin, and then the vas deferens was reached by a 22-G cannula contralateral to the testicular artery by using ultrasound guidance. Next, 0.5–1 mL of the local agent was administered just before touching the vas, visualizing the expansion surrounding the deferent duct, followed by 10 mL of the solution encircling it. Then, the technique was replicated on the contralateral side.

Surgery commenced 15 min after the block was performed. If the HR and MAP escalated more than 25% of baseline during skin incision, fentanyl bolus dose (0.5 μg/kg) was used, and the block was considered a failure.

Throughout the surgery, HR and MAP were noted every 15 min. When the procedure ended, sevoflurane was discontinued, and neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg) were used to undo the neuromuscular relaxation, and then laryngeal mask airway was removed.

After the operation, subjects were translocated to the post-anesthesia care unit (PACU) to recover and to be observed using the same intraoperative monitors. After regaining consciousness, pain was assessed using the VAS score and subsequently assessed for the severity of postoperative pain at 4-h intervals for a 24-h period to determine the first analgesic request time (between procedure termination and that of testicular pain sensation (VAS was ≥4)).

A similar postoperative analgesia protocol was used in both groups according to pain severity upon request. Acetaminophen 500 mg (Excedrin, Novartis Pharma, Egypt) two tablets every 6 h (no more than 8 tablets in 24 h). If the pain was severe, ibuprofen 400 mg (Brufen, Abbott, EGYPT) one tablet every 6 h (no more than 4 tablets per day) and 20 mg of omeprazole (Gastrazole, European Pharm IND, Egypt) once daily were given.

A surgical field score was requested from the surgeon who executed the procedure, using the surgical field rating (SFR) scale by Fromme *et al.*[14] (5 - massive uncontrollable bleeding, 4 - heavy but controllable bleeding that significantly interfered with dissection, 3 - moderate bleeding that moderately compromised surgical dissection, 2 - moderate bleeding – a nuisance but without interference with accurate dissection, 1 - bleeding so mild it was not even a surgical nuisance, and 0 - no bleeding and virtually bloodless field). The surgical field was graded as excellent, good, moderate, and bad as 4 = excellent - SFR scale 0, 3 = good - SFR scale 1, 2 = moderate - SFR scale 2 or 3, and 1 = bad – SFR scale 4 or 5. Furthermore, the occurrence of complications was observed and documented, including intraoperative hypotension, bradycardia, and postoperative nausea and vomiting, each managed correspondingly, including administering 10 mg of ephedrine if MABP <25% of the baseline, and atropine 0.6 mg given when the HR was <25% of the baseline. Furthermore, 4 mg of oral Ondansetron (Zofran, GlaxoSmithKline, Egypt) was administered to patients complaining of vomiting or nausea.

Following discharge, patients received a sheet to document their VAS score and the time of their first analgesic medication, analgesic consumption, and occurrence of adverse effects.

After 24 h, all participants were contacted by telephone and questioned about the documented data as well as their viewpoint on their satisfaction with the pain control using the following scale: 4 = excellent, 3 = good, 2 = fair, and 1 = poor.

The primary outcome was the time of postoperative testicular pain sensation, calculated as the time period elapsed from the termination of the procedure till the participant's first pain complaint. The secondary outcomes were the collective postoperative analgesic use requested during the first 24 h after the surgery is performed, as well as the incidence of intraoperative and postoperative complications that may arise as a result of this block, including hypotension, bradycardia, nausea and vomiting, and hematoma formation.

Statistical analysis

The sample size was calculated using G*Power 3.1 9.2 software (Universität Kiel, Germany). A previous study[4] showed that the main duration of SCB was 14.1 ± 6.9 h. Based on the hypothesis that adding neostigmine to 19 mL levobupivacaine 0.5% would prolong the duration of SCB by 30%, the minimal sample size calculated was 47 patients in each group to provide 90% power with a 2-tailed significance level at 5%. We included more patients (20%) for a final sample size of 112 participants to compensate for patients dropping out during the study.

Statistical analysis was performed using SPSS version 25 software (SPSS, Inc., Chicago, IL, United States). Categorical data were described as (number and %), whereas continuous data were described as (mean ± SD) where appropriate. Data that were not normally distributed were presented as (median (interquartile range)) and were analyzed using the Kruskal-Wallis test, as appropriate. Fischer's exact or Chi-square test was used for comparison between categorical variables, whereas continuous variables were compared using the independent sample *t*-test. To assess the time to first analgesic requirement between groups, Kaplan-Meier survival curves were created using MedCalc1 version 14.10.2. Statistical significance was set at $P < 0.05$.

Results

In total, 126 male participants scheduled for elective TESE procedure under general anesthesia were assessed for eligibility, while 14 participants were excluded due to not meeting or falling within inclusion criteria, surgery cancellation, or block failure. All 112 eligible patients (56 subjects in each group) completed the research and were analyzed [Figure 1].

When comparing both groups, the characteristics of participants were close, with no differences observed regarding demographic data (age, body mass index, ASA, and comorbidity) and operative data (surgical duration and time needed to perform the SCB) [Table 1].

The mean time to first requested analgesic was considerably detained in group N when compared to group C, with the values 480 ± 41.34 min versus 404 ± 34.14 min, independently, ($P < 0.05$). Moreover, the postoperative mean VAS was decreased at 8 h in group N compared to group C ($P < 0.05$). However, no remarkable variations among either studied group were found at 0,4,16, 20, or 24 h postoperatively [Figures 2-4].

Postoperatively throughout the first 24 h, there was a noticeable decrease in the mean acetaminophen and ibuprofen consumption in group N compared to group C, with the values 1196 ± 264 mg and 386 ± 445 mg versus 911 ± 332 mg and 236 ± 303 mg, respectively. However, no remarkable difference was found between the groups concerning the extent of hospitalization and the incidence of complications. In both groups, intraoperative surgeon satisfaction and postoperative patient satisfaction were achieved in all patients without major complaints [Table 2].

Table 1: Demographic and operative data of the two studied groups

	Control group (*n*=56)	Neostigmine group (*n*=56)	*P*
Age (year)	40.59±8.21	39.30±7.333	0.384
BMI (kg/m^2)	27.63±3.49	28.70±4.29	0.150
ASA I/II	37/19	42/14	0.407
Co-morbidity			
Hypertensive; *n* (%)	7 (12.5)	6 (10.7)	0.688
Asthmatic; *n* (%)	3 (5.4)	2 (3.6)	
Diabetic; *n* (%)	8 (14.3)	4 (7.1)	
Ischemic Heart disease; *n* (%)	1 (1.8)	2 (3.6)	
Duration of surgery (min)	49.18±13.34	46.95±7.76	0.281
Time needs to perform SCB (s)	208.71±74.27	197.05±44.25	0.316

Data are presented as mean±SD and n (%). SD – Standard deviation; BMI – Body mass index; SCB – Spermatic cord block

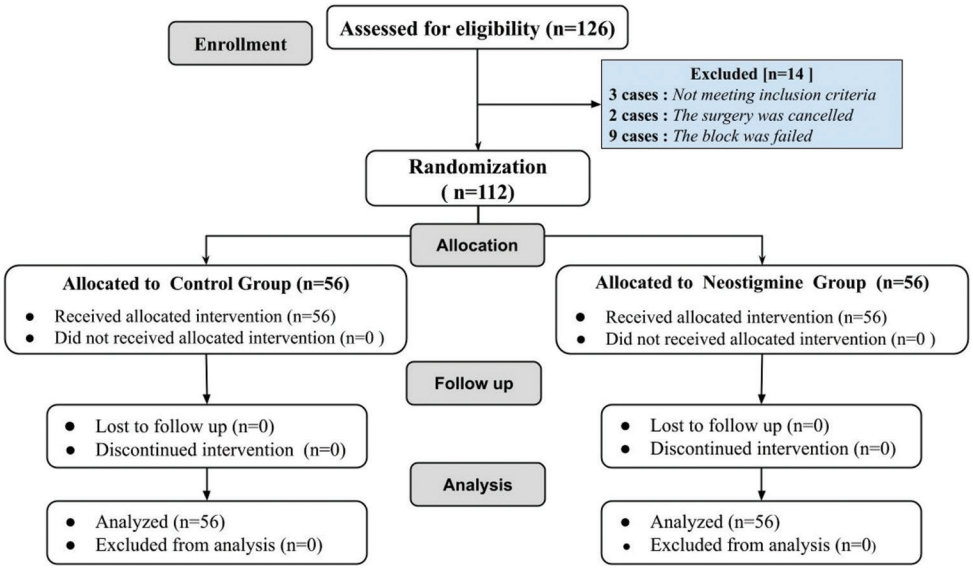

Figure 1: CONSORT flowchart of the participants

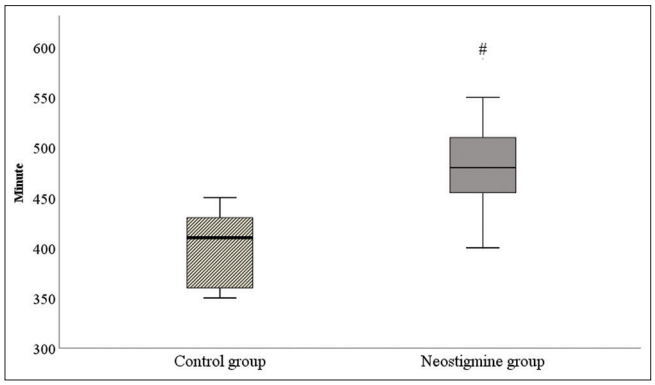

Figure 2: The postoperative pain-free time between the two studied groups. Data are presented as mean ± SD. *#Statistically significantly higher compared to the control group ($P < 0.05$)*

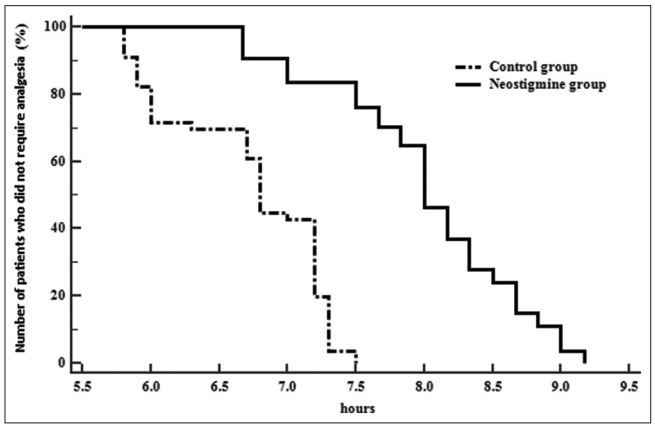

Figure 3: Kaplan–Meier survival analysis for time to first analgesia requirement between the two studied groups

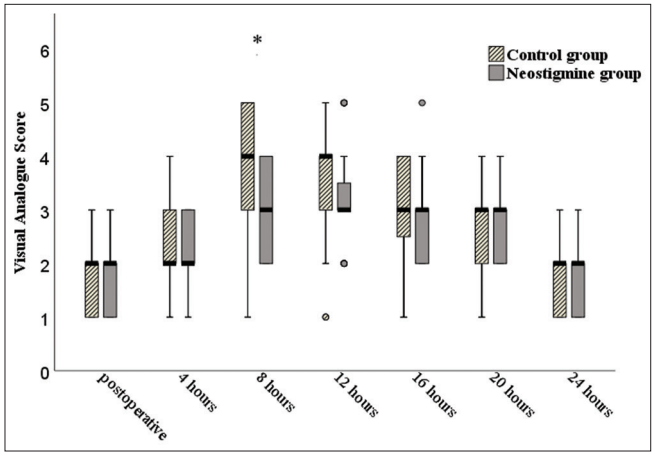

Figure 4: The postoperative visual analog score over time between the two studied groups. Data are presented as and median (IQR). **Statistically significantly lower compared to the control group ($P < 0.05$)*

Discussion

In this double-blinded control study, 500 μg of neostigmine was added to levobupivacaine 0.5% for SCB in subjects undergoing TESE operation. This caused a significantly delayed first analgesic requirement with lower pain intensity in the first 8 h postoperatively and decreased analgesia consumption both intraoperatively and postoperatively, without significant side effects.

Many patients undergoing TESE surgery experience acute postoperative pain; hence, potent analgesic strategies should be applied to control this problem. Oral analgesics have been preferred by many; however, they do not achieve the target level of analgesia. Parenteral opioids have also been considered, but in high doses, their drawbacks, including nausea, vomiting, and respiratory depression, were considered an obstacle. Regional analgesia is thought to be a promising alternative, especially the SCB, as it accomplishes the desired degree of postoperative pain relief, as well as providing pain control with the advantage of reducing the consumption of other parenteral analgesics. The technique of the SCB procedure was previously performed blindly until the help of ultrasound guidance was introduced recently, causing a witnessed increase in the success rate and a decrease in accidental vas deferens and testicular artery injuries.[15,16]

Regrettably, being a single-injection technique it requires the use of adjuvants to prolong its analgesic effect and increase its safety.[17,18] This study assessed the possible advantage of adding 500 μg of neostigmine to levobupivacaine 0.5%, which was favored over bupivacaine due to the reduced incidence of cardiovascular and neurologic drawbacks. Moreover, neostigmine was chosen due to the lack of sufficient information about its effectiveness as an adjuvant to local anesthesia. Although much research has been performed to understand its peripheral mechanism, it remains unclear. However, some theories explained its augmenting effect when added to local anesthetics, including a theory that claimed its action as an anticholinesterase drug that inhibits the acetylcholine breakdown, increasing its level, leading to the stimulation of muscarinic receptors in the peripheral nerve endings, which in turn causes neuronal hyperpolarization and cholinergic-mediated anti-nociception activation by activating the nitric oxide-cGMP pathway.[7,19] Another theory suggested that acetylcholine has an effect on the sensory regulatory mechanism by its receptors that exist in the ganglia of the neurons, under normal conditions.[20] Consequently, adding neostigmine to a local anesthetic agent has been controversial.

Our study findings agreed with Elbahrawy K and El-Deeb,[11] who tested the response of adjoining neostigmine to bupivacaine in supraclavicular brachial plexus block and showed a reduced need for rescue analgesics postoperatively with fast onset of sensory and motor functions, without significant side effects. Yadav RK *et al.*,[21] Bouderka MA *et al.*,[22] and Bone HG *et al.*[23] added neostigmine to lignocaine, bupivacaine, and mepivacaine in brachial plexus block, respectively. All

Table 2: The postoperative analgesic consumption, scoring of postoperative patient satisfaction, incidence of complications, and hospital stay between the two studied groups

	Control group (*n*=56)	Neostigmine group (*n*=56)	*P*
Acetaminophen			
Number of patients; *n* (%)	56 (100%)	56 (100%)	1
Total amount of acetaminophen consumption (mg)	1196.43±264.21	910.71±331.76*	<0.001
Ibuprofen			
Number of patients; *n* (%)	38 (67.9%)	26 (46.4%)*	0.035
Total amount of postoperative	385.71±444.53	235.71±302.97*	0.039
Ibuprofen consumption (mg)			
Surgical field score	3 (2-4)	3 (3-4)	0.631
Post-operative patient satisfaction	4 (3-4)	4 (3-4)	0.829
Hospital stays (h)	6.14±0.55	6.25±0.94	0.464
Intraoperative complication			
Hypotension *n* (%)	2 (3.6)	2 (3.6)	0.900
Bradycardia *n* (%)	2 (3.6)	3 (5.4)	
Postoperative complication			
Nausea and vomiting *n* (%)	4 (7.1)	5 (8.9)	0.801
Hematoma (%)	2 (3.6)	1 (1.8)	

*Data are presented as mean±SD, median (IQR), and n (%); SD – Standard deviation. Surgical field graded as 4=excellent, 3=good, 2=moderate, 1=bad. Post-operative Patient satisfaction as: 4=excellent, 3=good, 2=fair and 1=poor. *Statistically significantly lower compared to the control group (P<0.001)*

concluded the beneficial result of adjoining neostigmine to local agents on the postoperative analgesic duration.

On a different note, some examined using neostigmine as an adjunct to intravenous regional analgesia medication, as in studies by Sethi D and Wason[24] and Kang KS *et al.*,[25] where neostigmine was added to ropivacaine, and another by Turan *et al.*,[26] where it was added to prilocaine. Despite showing results that resemble those found in our study, they were conducted using different agents with different doses and a different number of subjects.

Nevertheless, some studies failed to find any benefits from adding neostigmine to local anesthesia through peripheral mechanisms. A study used 1 mg of neostigmine with lidocaine in intravenous regional anesthesia in upper limb surgery, finding no differences in pain control, which could be attributed to the type of patient or the absence of inflammatory activity and an intact neuronal lipid covering.[27] In another study, it was used with axillary plexus block and found no change in postoperative analgesic duration, with increased side effects.[13]

Some limitations were recognized in this study, including the small sample size used; thus, a larger number of patients could be considered in future research. Moreover, testing different doses of the agents used to ensure the drug efficacy and determine its proper safe dose for patients. Finally, the sensorial blocked area was not assessed as the block was performed after general anesthesia induction to maintain the double-blind nature of the study.

Conclusions

Adding neostigmine as an adjuvant to local anesthetic solution in spermatic cord block is a promising choice to prolong the time for the first analgesic requirement postoperatively and reduce perioperative analgesia consumptions without significant side effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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