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Effect of adding neostigmine to bupivacaine for ultrasound-guided supraclavicular brachial plexus block in forearm surgeries a randomized, blinded, controlled study

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Abstract

Background: In our study, we investigated the effect of adding neostigmine to local anesthetic on the supraclavicular brachial plexus block. Patients and Methods: This prospective, randomized, blinded controlled experiment included 80 patients of either sex with an ASA I or II physical status who were planned for forearm operations under ultrasound-assisted supraclavicular brachial plexus block. Participants were separated randomly into two groups and given a supraclavicular block with 25 mL of 0.5% bupivacaine and 1 mL of 0.9 % saline for the control group and 25 mL of 0.5% bupivacaine and 1 mL of neostigmine (0.5mg) for the neostigmine group. Results: In the neostigmine group, sensory and motor blockade began earlier and lasted longer than in the control group. The neostigmine group took substantially longer to seek their first analgesia. The neostigmine group used fewer analgesics in total. At 1, 2, 4, and 6 hours, the neostigmine group had statistically reduced VAS scores than the control group. Conclusion: Patients undergoing forearm procedures benefit from the usage of neostigmine in addition to bupivacaine in ultrasound-assisted supraclavicular brachial plexus block because it reduces the onset of sensory and motor block and lengthens its duration. These results were clear with a dosage of (0.5 mg).

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Supraclavicular brachial plexus block; neostigmine

1. Introduction

Most procedures on the upper limbs are carried out using the brachial plexus block. Without causing any systemic adverse impacts, peripheral nerve blocks prolong analgesia in the postoperative period and also offer good anesthesia during surgery (Bruce et al., 2012) [1].

The supraclavicular block is the optimum choice for operations on the arm and forearm, from the lower humerus to the hand. A block at this point has the highest likelihood of blocking all of the branches since the brachial plexus is more compact at the level of the trunks. This leads to quick beginning times and excellent success rates for upper extremity surgery and analgesia, except for the shoulder (Mian et al., 2014) [2].

There is constantly a search for medications that may be used as adjuvants to the regional nerve blocks and extend the analgesic duration with fewer adverse consequences. Neostigmine is used intra-articularly after knee arthroscopy and in conjunction with local anesthetics during regional anesthesia. Neostigmine as para sympathomimetic medication reversibly blocks the cholinesterase enzymes. By preventing acetylcholine breakdown, it activates both nicotinic and muscarinic receptors. One of the many neurotransmitters that affect how pain is processed at the spinal cord level is acetylcholine. Acetylcholine is released by pain and also released when opioid and alpha-2 adrenergic receptors in the brain stem and spinal cord are activated. Neostigmine increases analgesia by preventing acetylcholine from degradation (Alagol et al., 2005) [3].

Endogenous acetylcholine is increased by inhibition of spinal cholinesterase, it is released by intrinsic cholinergic neurons in the dorsal horn of the spinal cord, Naguib and Yaksh 1997 [4] argued that the spinal M1 and/or M3 receptor subtypes are likely to mediate the analgesic activity.

The control of nitric oxide pathways and neuronal hyperpolarization produce peripheral cholinergic antinociception according to Vitro studies, and other research has proven the presence of acetylcholine receptors in peripheral neurons. Acetylcholine causes analgesia by increasing cyclic GMP through Nitric oxide production (Ferreira et al., 1990) [5].

The substantia gelatinosa of the spinal cord contains muscarinic receptors, which are hypothesized to be responsible for this analgesic activity, which is not brought on by nicotinic or opioid receptor activation. (Solomon et al., 1994) [6].

According to Varas et al., 2000 [7] study, petrosal ganglion neurons soma have acetylcholine receptors, supporting the hypothesis that peripheral sensory processing may be acetylcholine-related.

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Neostigmine provides analgesia by preventing the spinal cord's Acetylcholine from breaking down when administered intrathecally or epidurally (Lauretti et al., 1996 [8] & Almeida et al., 2003 [9]). However, some studies did not find any benefit from adding neostigmine to intravenous regional anesthetic and peripheral nerve blocks (Van Elstraete et al., 2001 [10] & McCartney et al., 2003 [11]), and other research showed a good effect of adding neostigmine to peripheral nerve blocks (Elbahrawy and El-Deeb 2016) [12].

In this investigation, we investigated the effects of combining neostigmine with bupivacaine on the initiation and length of sensory and motor block, postoperative analgesia, and possible adverse consequences during ultrasound-guided supraclavicular brachial plexus blocks in forearm operations.

2. Patients and methods

2.1. Ethical approval and trial registration

The Faculty of Medicine, Minia University, Research Ethics Committee (FMREC) gave its clearance for the research, and all procedures were carried out in compliance with its relevant policies and procedures (approval number: 72-7-2018). ClinicalTrials.gov has this study listed as NCT04000100.

2.2. Patient recruitment

This randomized controlled blind clinical study took place at Minia University Hospital. The research included 83 patients who underwent supraclavicular brachial plexus blocks for forearm procedures. The patients were of both sexes, ≥18 years old, and ASA I–II.

We excluded from our investigation any patient who refused the operation, complained of any bleeding tendency, was taking oral anticoagulants, had any brachial plexus-related neurological deficits, was allergic to local anesthesia, had local infections at the injection site, or was taking any sedatives or antipsychotics.

2.3. Preparation of the studied medications

In this trial, the participants, the data analyst, and the clinical investigator were all kept blind about the study grouping. The supervisor, who was not a member of the anesthetic or surgical teams, prepared all drugs in identical sterile-covered bottles. There were 83 bottles in all, each with a number from 1 to 83. Coded as I or II. At the end of this research, these codes were opened and the groups were as follows:

Code I (control group): received 25 mL of 0. 5% bupivacaine and 1 mL of 0.9% normal saline.

Code II (neostigmine group): received got 25 mL of 0. 5% bupivacaine and 1 mL neostigmine (0.5 mg) Epistigmin (neostigmine methyl sulfate 0.05% Egyptian international pharmaceutical industries company (EIPICO).

2.4. Preoperative evaluation and planning

There was a thorough evaluation of clinical history. Heart rate, blood pressure, and a physical assessment of the chest, heart, abdomen, injection site, and other systems were performed as part of the general assessment. CBC, Coagulation profile, renal, and liver function tests were done. An explanation of the visual analogue scale was performed. A 20 G IV cannula was placed in a peripheral vein of the unaffected limb as soon as the patient entered the operating room, and routine monitoring started.

3. Outcomes assessed

3.1. Primary outcome measures

3.1.1. The onset of sensory blockage

Was evaluated Using a pinprick test.

3.1.2. The onset of motor blockage

Measured thumb abduction, thumb adduction, thumb opposition, and elbow flexion (radial nerve, ulnar nerve, median nerve, and musculocutaneous nerve; respectively) utilizing a 3-point scale.

Grade 0: Full finger, wrist, and elbow flexion and extension.

Grade 1: Reduced motor function, limited to finger movement only.

Grade 2: Completely blocked, unable to move the fingers.

The duration between administering the full dose of local anesthesia and the onset of the complete motor block (grade 2) was measured in minutes as the onset of motor blockage.

3.1.3. The length of the sensory blockage

The interval between total sensory blocking and total anesthetic resolution on all neurons.

3.1.4. The length of the motor blockage

A measure of how long it takes for hand and forearm motor functioning to fully recover (grade 0) after a full motor block.

3.2. Secondary outcome measures

3.2.1. Visual analogue scale

VAS was used to determine the severity of the pain. The VAS is a 10-cm-long straight line with the bottom point representing "no pain" and the highest point

representing "the greatest agony you may experience" (10 cm). Patients were instructed to draw a horizontal mark across the line where it showed how much pain they were experiencing. We provide paracetamol (Perfalgan®) 1 gm. IV drip as an analgesic when VAS is more than or equal to 4 cm. Patients were asked to assess their level of discomfort at 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours after surgery.

3.2.2. First analgesic request time

How many hours pass after a supraclavicular brachial plexus block is administered before the patient requires their first dose of painkillers. It was evaluated every half an hour for four hours, then every two hours for a full day.

3.2.3. 24-hour total analgesic dosage required

The total quantity of paracetamol (Perfalgan®) administered to the patient as rescue analgesia over 24 hours.

3.2.4. Adverse effects

Any negative effects, including bradycardia, nausea, vomiting, local hematoma, hemothorax, pneumothorax, intravascular injection, and toxicity from local anesthetics symptoms, were noted in the procedure and for 24 hours.

4. Block technique

Patients were lying supine with their heads rotated 45 degrees to the other side. The assistant gently adducted the patient's ipsilateral arm, keeping the shoulder down with a flexed elbow. The brachial plexus was seen utilizing an ultrasonic probe with a linear multi-frequency 6–13 MHz transducer (USA, SONOSITE M-TURBO) after sterile skin preparation.

The block was carried out using a 20-gauge, 50-mm Stimuplex A, B Braun, Melsungen, Germany regional block needle. After injecting half of the prepared local anesthetic combination with either 0.5 ml of saline or neostigmine into the "corner pocket", the needle was moved cranially toward the neural clusters. The other quantity of the medication was deposited using the repeated injection procedure. To enhance the local anesthetic distribution, a 3-min massage was done.

Patients were evaluated for sensory and motor blockage initiation, length, and postoperative analgesia after the drug administration, as well as for any medication side effects or procedure problems. Postoperatively, VAS for pain was used to evaluate the effectiveness of analgesia. The time from the local anesthetic injection to the first analgesic need was used to determine the duration of analgesia. During and after surgery, all patients were monitored for any adverse effects.

4.1. Sample size and statistical analysis

Before the trial, a power calculation using information from a pilot study was employed to establish the necessary number of patients in each group. employing the G Power 3.1 9.2 program, it was found that 40 patients within every group would provide 99% power for a one-way ANOVA test at the value of 5% significance for the onset of sensory block.

Statistical Package for the Social Sciences (SPSS), Version 22, was utilized to examine the data. When displaying quantitative variables, the mean and standard deviation were utilized. Frequency distributions were employed to illustrate qualitative variables. For assessing qualitative variables between two groups, the Chi-square test was applied. For analyzing parametric quantitative variables of two groups, an independent sample t-test was employed. Assessing non-parametric quantitative variables between two groups was done utilizing the Mann-Whitney test. For all meaningful tests, a cut-off probability of less than 0.05 was applied.

5. Results

Only 95 individuals who satisfied the inclusion criteria were assigned to the trial out of a total of 120 patients who were evaluated for eligibility between July 2018 and January 2019. Twelve patients declined to take part in the investigation. 83 patients were randomized, 42 in the control group and 41 in the neostigmine group. 2 patients in the control group and 1 in the study group had block failure (they had general anesthesia). So we analyzed 80 patients, forty in each group Figure 1.

Age, sex, weight, ASA classification, and surgery length were determined to be statistically insignificant between the two groups (Table 1).

Between the two groups, there was a significant difference relating to the start of the sensory and motor block, which occurred more quickly in patients who took neostigmine (Table 2, Figure 2).

According to the length of the sensory and motor blocks, there was a significant difference between the two groups, with the neostigmine group's sensory and motor blocks lasting longer than those of the control group (Table 3, Figure 3).

The median time of 1st analgesic request (hour) was significantly longer in the neostigmine group (16.1 ± 2.5) in comparison to the control group (11.9 ± 2 hr.) and total paracetamol requirements in the neostigmine group were significantly less than the control group (Table 3, Figures 4 and 5).

According to VAS, it was significantly lower in the neostigmine group at 1, 2, 4, and 6 hours (Table 4, Figure 6)

There was no difference between the two groups regarding the side effects as the incidence of nausea, vomiting, and bradycardia was not statistically different.

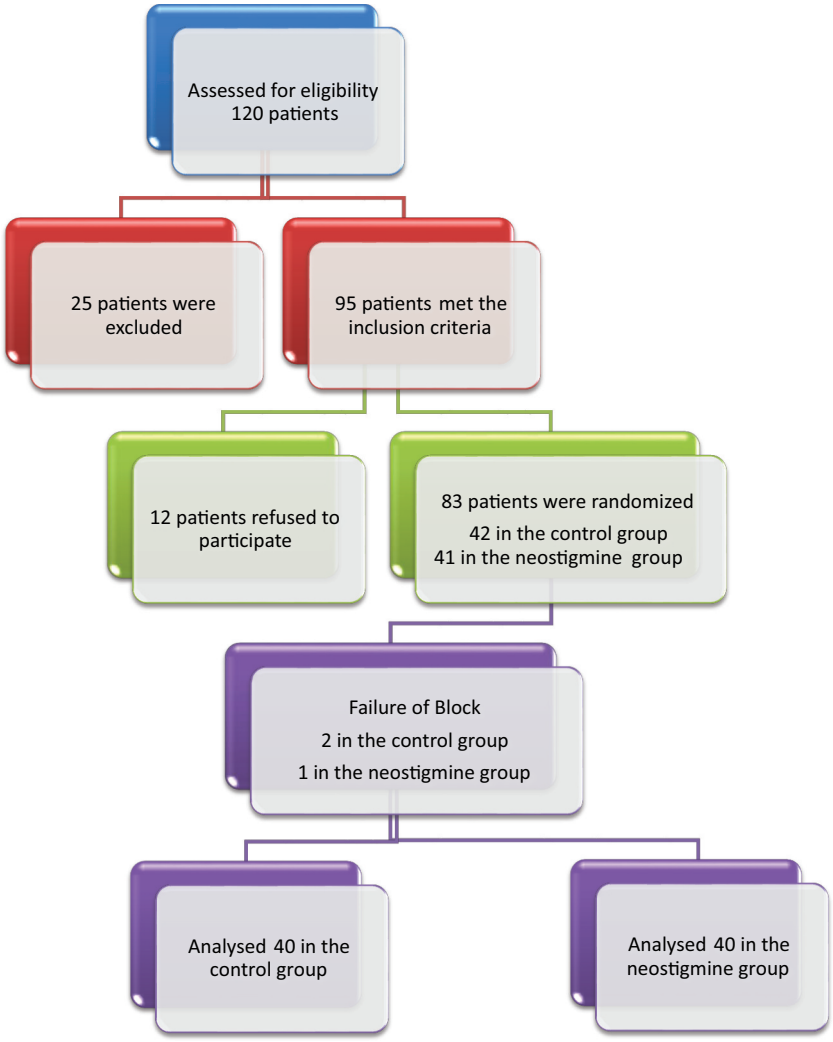

Figure 1. Consort flow chart.

Table 1. Demographic and clinical variables of the investigation groups.

Variables	Control group	Neostigmine group	P – value
Age (Years)	18–75 39.7 ± 17.5	18–76 39.45 ± 18.9	0.937
Sex	27 (67.5%)	30 (75%)	0.459
Male	13 (32.5%)	10 (25%)	
Female			
Weight (kg)	60–90 75.7 ± 7.7	60–95 75.9 ± 8.9	0.883
ASA	25 (62.5%)	26 (65%)	0.816
ASA I	15 (37.5%)	14 (35%)	
ASA II			
Duration of operation (min)	59–85 45 ± 10.3	58–88 43.4 ± 12.4	0.523

Data are presented as means, standard deviations, numbers, percentages, and ranges.
Comparing quantitative data between the two groups using an independent sample t-test.
The Chi-square test was used for Sex and ASA.

Table 2. Onset of sensory and motor blocks.

Variables	Control group	Neostigmine group	P – value
The onset of sensory blockade (min)	(10–15) 11.3 ± 0.8	(8–14) 9.4 ± 1.8	0.005
The onset of motor blockage (min)	(12–23) 14.7 ± 2.4	(11–17) 11.2 ± 1.5	0.001

Data are expressed as mean ± standard deviations and range.
Comparing quantitative data between the two groups using an independent sample t-test.

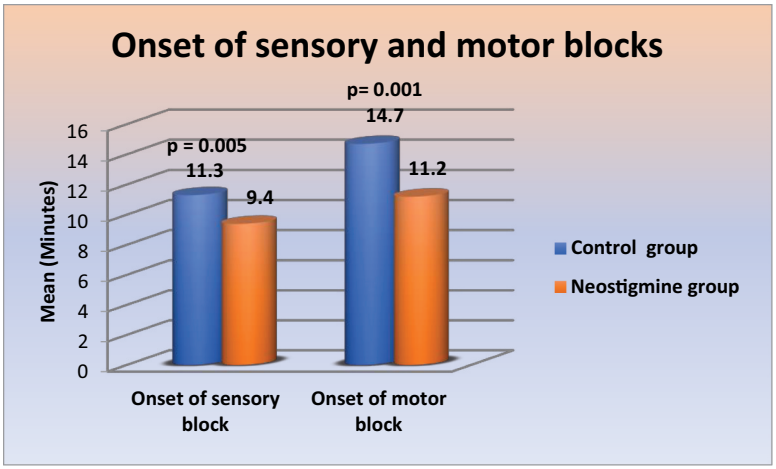

Figure 2. Onset of sensory and motor blocks.

Table 3. Onset of sensory and motor recovery and analgesic requirement.

Variables	Control group	Neostigmine group	P – value
The onset of sensory recovery (hour)	8–13 10.45 ± 1.1	11–14 12.4 ± 0.8	<0.001
The onset of motor recovery (hour)	5–13 10.02 ± 1.4	11–14 12.9 ± 1	<0.001
1st analgesic request (hour)	2–15 11.9 ± 2	4–18 16.1 ± 2.5	<0.001
Total analgesic consumption (gram per person)	1–3 1.25 ± 0.49	1–2 1.02 ± 0.15	0.007

Data are expressed as mean ± standard deviations and range.
Comparing quantitative data between the two groups using an independent sample t-test.

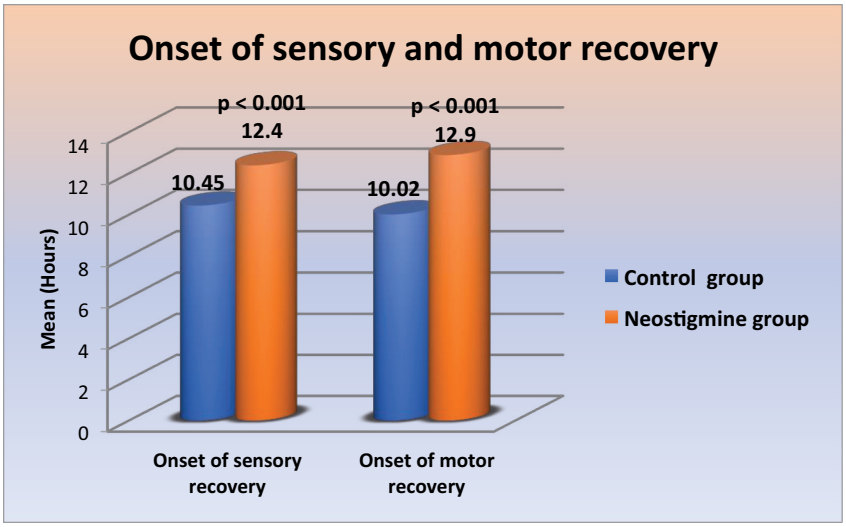

Figure 3. Onset of sensory and motor recovery.

As regards inadvertent intravascular injection, neurological manifestations, local anesthetic toxicity, hemothorax, and pneumothorax we didn't record any cases.

6. Discussion

In this research, we studied the effect of an ultrasound guiding supraclavicular brachial plexus block utilizing 0.5% bupivacaine alone or with 0.5 mg of neostigmine. The primary conclusion of this research was that, in contrast to the control group, the start of sensory and motor blockade was accelerated by the administration of 0.5 mg of neostigmine, a reduction in the need for analgesics, and an extended duration of analgesia. The neostigmine group seemed to perform better than the control group in terms of the rapid start of the action, length of analgesia, and the sum of analgesics required.

Therefore, longer analgesic duration in the neostigmine group compared with the control group in our research may be caused by the activation of muscarinic

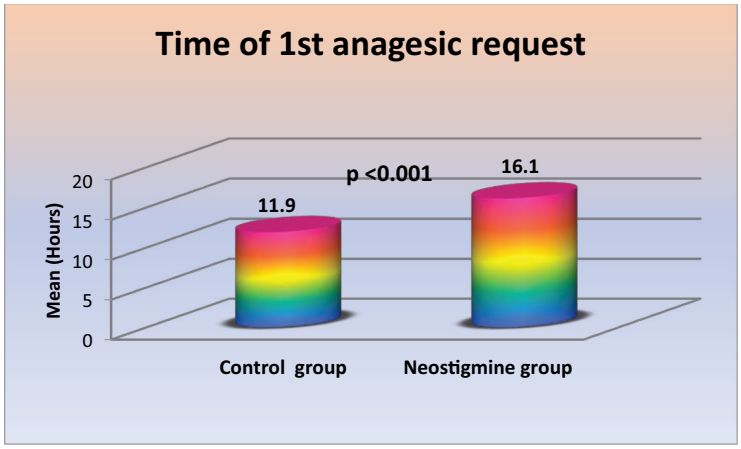

Figure 4. 1st analgesic request.

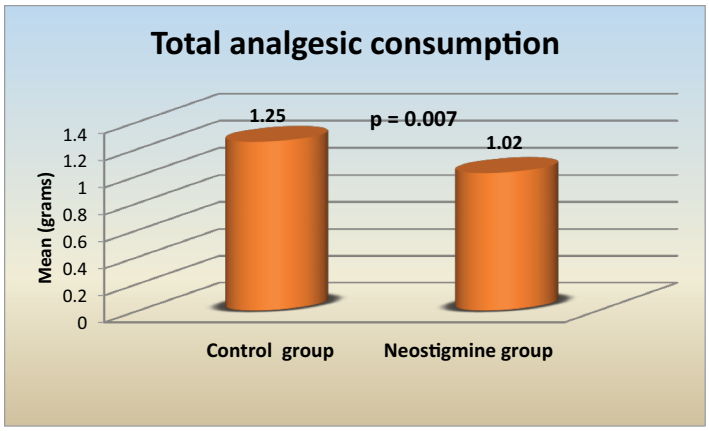

Figure 5. Total analgesic consumption.

Table 4. Postoperative visual analogue scale.

Variables	Control group	Neostigmine group	P – value
VAS 1 h	0–2 0.9 ± 0.7	0–2 0.55 ± 0.68	0.027
VAS 2 h	0–2 1.1 ± 0.63	0–2 0.725 ± 0.72	0.015
VAS 4 h	0–4 1.3 ± 1.06	0–4 0.75 ± 1.08	0.025
VAS 6 h	0–4 1.65 ± 1.46	0–4 1.05 ± 1.197	0.048
VAS 8 h	0–4 1.9 ± 0.63	0–4 1.85 ± 0.53	0.703
VAS 12 h	2–5 2.8 ± 1.4	2–5 2.35 ± 0.89	0.09
VAS 16 h	2–5 2.8 ± 1.09	2–5 3.05 ± 1.4	0.376
VAS 20 h	2–5 2.6 ± 0.9	2–5HT 2.9 ± 1.5	0.281
VAS 24 h	2–5 2.7 ± 1.06	2–5 2.5 ± 1.26	0.445

Data are expressed as mean ± standard deviations and range.
Mann-Whitney test was used.

receptors in peripheral neurons, which may have an antinociceptive effect.

In line with our research Elbahrawy and El-Deeb 2016 [12] examined the results of adding neostigmine to an ultrasound-guided supraclavicular brachial plexus block in patients with chronic renal failure. Three groups of 93 patients with chronic renal failure were randomly assigned; the control group got 20 ml of 0.5% bupivacaine mixed with 10 ml of ordinary saline, while the two neostigmine groups had 0.25 and 0.5 mg of neostigmine, respectively. They discovered that in individuals who get 0.5 mg of neostigmine, the onsets of sensory and motor blockage were greatly shorter. Sensory and motor blockade lengths were

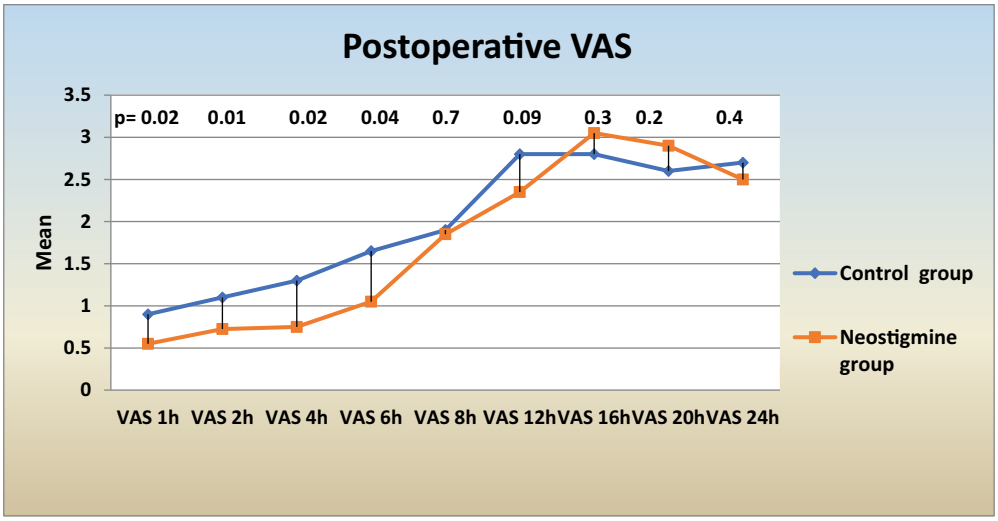

Figure 6. Postoperative VAS.

similar among the three groups. The need for postoperative rescue analgesics and the average pain score were lower in the neostigmine group 0.5 mg compared to the neostigmine group 0.25 mg and the control group. They concluded that the supraclavicular brachial plexus block when neostigmine was added, there was a quick start of sensory and motor blockade, and no major adverse effects.

The results of our investigation were found to be similar to those of Bouderka et al., 2003 [13], 90 patients planned for orthopedic or cosmetic surgeries were divided into 3 groups at random and given either saline solution (1 ml), 500 mcg (1 ml) of neostigmine in the axillary plexus, or 3.500 mcg of neostigmine subcutaneously. With the addition of Neostigmine (500 mcg) to Bupivacaine during an axillary brachial plexus block, the VAS score and the need for postoperative analgesics were both significantly reduced.

In agreement with this, Gentili et al., 2001 [14] revealed that in patients having arthroscopic meniscus repair, intra-articular injection of 500 mcg of neostigmine caused a substantial variation in postoperative pain severity, total intake of IV rescue analgesics, and first acquisition for analgesia.

Abdelhamid et al., 2021 [15], To ascertain the analgesic efficacy of ketamine and neostigmine as additives to local anesthetic in ultrasound-guided Serratus anterior plane block, 90 female participants underwent modified radical mastectomy under combined general anesthesia and preoperative Serratus Anterior Plane Block were analyzed. The patients were divided into three groups: the neostigmine group got 30 ml of bupivacaine 0.25% plus 1 ml of neostigmine (500 mcg); the ketamine group received 30 ml of bupivacaine 0.25% plus 1 ml of ketamine (50 mg), and the control group got 30 ml of bupivacaine 0.25% plus 1 ml of normal saline. The addition of 50 mg ketamine to 0.25% bupivacaine throughout preoperative ultrasound-guided Serratus Anterior Plane Block combined with general anesthesia lowered the 24 hours following surgery morphine consumption and the intraoperative fentanyl needed, while the addition of 500 mcg neostigmine lowered the intraoperative fentanyl needed.

In disagreement with our results, Van Elstraete et al., 2001 [10] 34 ASA I or II patients having an elective ambulatory carpal tunnel surgery were the subject of the study. The median nerve was located utilizing a peripheral nerve stimulator and an axillary brachial plexus block was done. Epinephrine 5 mcg mL-1 and 1.5% lidocaine 450 mg were given to all patients. Patients were split into one of two groups at random. In one group, 500 mcg of neostigmine was added, while in the other, 1 mL of saline was added. They concluded that neostigmine does not appear to be of clinical value for peripheral nerve blocks after discovering that the need for additional analgesia did not substantially vary between groups, as well as that VAS scores and the incidence of adverse impacts did not substantially differ.

According to our research, adding 0.5 mg of neostigmine to a brachial plexus block using 0.5% bupivacaine had no discernible negative effects. As there was no difference between the two groups regarding the side effects as the incidence of nausea, vomiting, and bradycardia was not statistically different. Our results were supported by the study of Elbahrawy and El-Deeb 2016 [12]. They reported that there were no significant side effects from the addition of 250 or 500 mcg neostigmine to brachial plexus block with 0.5% bupivacaine in end-stage renal failure patients

Also, the findings of Yang et al., 1998 [16] and Gentili et al., 2001 [14] revealed no major negative effects related to 0.5 mg neostigmine treatment intraarticularly. They also observed that there was no statistically substantial variation in the occurrence of

nausea, vomiting, or bradycardia in patients who get neostigmine or not.

In contrast to our findings, Bouaziz et al. 1999 [17] revealed that the addition of neostigmine to a mepivacaine axillary plexus block resulted in a comparatively high prevalence of adverse effects. This might be explained by the study's lack of utilization of ultrasound guidance.

7. Conclusion

Patients undergoing forearm procedures benefit from the usage of neostigmine in addition to bupivacaine in ultrasound-assisted supraclavicular brachial plexus block because it reduces the onset of sensory and motor block and lengthens its duration. These results were clear with a dosage of (0.5 mg).

Disclosure statement

No potential conflict of interest was reported by the authors.

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