Journal of Advances in Medicine and Medical Research

33(16): 155-165, 2021; Article no.JAMMR.70853
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Comparison between Morphine and Hyaluronidase Added to Local Anesthetic in Sonar Guided Supraclavicular Brachial Plexus Block; Randomized Double Blinded Controlled Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1631011
Editor(s):
(1) Dr. Rui Yu, University of North Carolina at Chapel Hill, USA.
Reviewers:
(1) Devyani Desai, Medical College, India.
(2) Somchai Amornyotin, Mahidol University, Thailand.
Complete Peer review History: https://www.sdiarticle4.com/review-history/70853

Original Research Article

Received 15 May 2021
Accepted 21 July 2021
Published 22 July 2021

ABSTRACT

Background: Huge volumes of local anaesthetics used in conventional blocks may be associated with complications. Hyaluronidase is an enzyme that hydrolyses hyaluronic acid in the tissue. It has been shown to aid the spread of local anaesthetics (LA) through tissue. The aim of this study was to compare between the addition of morphine or hyaluronidase to local anaesthetic in sonar guided supraclavicular brachial plexus block regarding the onset and duration of the block, postoperative analgesia and the total analgesic requirements in the first 24 hours.
Patient and methods: Seventy-five patients of American Society of Anaesthesiologists (ASA) physical status I & II, aged 18-60 years, scheduled to acute or elective elbow, forearm or hand surgery under sonar guided supraclavicular brachial plexus block at Tanta University Hospital were randomly allocated into three equal groups; Group I (Control group) received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 2 ml normal saline, group II (Morphine group) received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 5 mg morphine in 2 ml normal

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saline and group III (Hyaluronidase group) received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 1500 units of hyaluronidase in 2 ml normal saline. The onset of sensory and motor block, duration of sensory and motor block, postoperative VAS, time to first rescue analgesia, total morphine consumption and possible side effects were recorded.
Results: Onset of the sensory block and motor block was significantly shorter in the hyaluronidase group than control group and morphine group. Duration of the sensory block and motor block was significantly prolonged in morphine group than hyaluronidase group & control group. VAS started to increase at 6 hours in the control group, at 10 hours in morphine group and at 8 hours in hyaluronidase group. Time to first rescue analgesia was significantly prolonged in morphine group than control group and hyaluronidase group. Total analgesic consumption of morphine was significantly lower in morphine group than control group and hyaluronidase group.
Conclusion: Morphine was superior to hyaluronidase as regarding to improving the post-operative pain. The incidence of complications was nil and self-limited in the three groups.

Keywords: Hyaluronidase; morphine; supraclavicular brachial plexus block; visual analog scale.

1. INTRODUCTION

Different methods of regional anesthesia are used in upper extremities for brachial plexus nerve block [1]. The supraclavicular level is an ideal site to achieve anesthesia of the entire upper extremity just distal to the shoulder as the plexus remains relatively tightly packed at this level, resulting in a rapid and high quality block [2].

Moreover, a huge volume (30–40 mL) of local anesthetics used in conventional blocks may be associated with complications such as phrenic nerve palsy, Horner's syndrome, and systemic toxicity [3]. Many studies have examined the use of various additives to decrease dose and systemic toxicity of local anesthetic and increase quality of regional blocks [4].

These additives include opioids, midazolam, alpha 2 agonists, ketamine, neostigmine, hyaluronidase, bicarbonate, calcium channel blockers, dexamethasone and dexmedetomidine but none has conclusive results [5].

Several authors have investigated the efficacy of injecting opioids into the brachial plexus sheath, but the results remain inconclusive. While others didn't observe any benefit from adding opioids [6]. Morphine is an opioid receptor agonist, can be administered by intravenous, intramuscular, intrathecal, epidural routes or added to local anesthetic for the relief of pain. Its main effect is binding to and activating the μ-opioid receptors in the central nervous system and in the superficial dorsal horn of the spinal cord. Morphine is also a κ-opioid and δ-opioid receptor agonist. κ-Opioid's action is associated with spinal analgesia and psychotomimetic effects. δ-Opioid is thought to play a role in analgesia [7].

Hyaluronic acid is widely found in the extracellular connective tissue matrix [8]. Hyaluronidase is an enzyme that hydrolyses hyaluronic acid in the tissue. It has been shown to aid the spread of local anesthetics (LA) through tissue. It is postulated that it achieves this by a reversible depolymerizing effect on hyaluronic acid. It has also been demonstrated that it raises the pH of a LA preparation, thereby contributing to the efficacy of LA blockade [9].

The aim of this study was to compare between the effects of addition of morphine or hyaluronidase to local anesthetic during sonar guided supraclavicular brachial plexus block. The primary outcome was the onset and duration of the block. While the secondary outcomes were the postoperative analgesia, time to 1st rescue analgesia and the total analgesic requirements in the 1st 24 hours.

2. PATIENTS AND METHODS

This prospective double blinded randomized controlled study was conducted in orthopedic & general surgery departments in Tanta University Hospital from August 2019 to August 2020 on 75 patients, American Society of Anesthesiologists (ASA) physical status I & II, age 18-60 years, scheduled to upper limb surgery below the shoulder.

Patients unable to cooperate, those had allergy to any drugs used in the study, peripheral neuropathy, neurological disorders, local skin infection at the site of injection, coagulopathy,

patient refusal and a history of drug dependency were excluded from the study.

Randomization by computer generated random numbers concealed in 75 sealed envelopes technique classified into three groups 25 patients each. Group I (Control group): received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 2 ml normal saline. Group II (Morphine group): received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 5 mg morphine diluted in 2 ml normal saline. And group III (Hyaluronidase group): received 20 ml containing 9 ml bupivacaine 0.5% and 9 ml lidocaine 2% plus 1500 units of hyaluronidase diluted in 2 ml normal saline. The solution was prepared by a person and was injected by another one for blindness of the study.

Preoperatively, medical history, physical examination, and indicated investigations were performed. On arrival to the preparation room, basic monitors including electrocardiogram (ECG), noninvasive blood pressure, and pulse oximetry were attached to the patient. An intravenous (IV) line was inserted in the contralateral hand with 18-gauge cannula and 6 mL/kg/h crystalloid was infused. Prior to the block, the patient received intravenous midazolam 1mg and intravenous fentanyl 0.5µg/kg and O2 via a nasal cannula at a rate of 1-2 liters/ minute was attached.

The patient was supine with the head turned to the opposite side and the arm was pulled down gently using ultrasound machine (PHILIPS-CX50, extreme edition, Philips, Finland) with a 12 MHz linear probe. The supraclavicular fossa was sterilized with povidone iodine or chlorhexidine 2%.

The linear probe was placed in the supraclavicular region transversely in the mid clavicular point, aimed caudally to the thorax. The brachial plexus appeared as 3 hypoechoic circles with hyperechoic outer rings (a grape like cluster) lateral and superior to the subclavian artery between the anterior and middle scalene muscles. The subclavian artery was visualized as a round pulsating hypoechoic structure. The first rib was visualized as a hyper echoic line which was used as a landmark, to decrease risk of pneumothorax.

A small amount of subcutaneous local anesthetic (L.A) was injected lateral to the lateral aspect of the probe. Then the 18- gauge block needle was flushed with the relevant L.A loaded on the extension tubing. The needle was held by the dominant hand and the needle tip was inserted perpendicular to the skin in-plane from posterior to anterior and from lateral to medial and directed toward the interscalene groove. The needle was then adjusted to a shallow angle to visualize the shaft and tip in the ultrasound window. The needle was advanced carefully toward the plexus trying to visualize the entire structure. When the needle tip was in the desired position, 2 ml of L.A solution was injected causing an expansion in the plexus diameter with a hypoechoic substance then 10 ml of LA was injected deep to the brachial plexus after negative aspiration. The needle was then retracted to the skin and readvanced at a shallow angle, directing the needle to the superficial aspect of brachial plexus. Another 10 ml of LA was injected superficial to the brachial plexus after negative aspiration. The needle position might be adjusted after each aliquot if required in order to bathe all the nerves in the plexus.

The sensory block was initially tested by an independent observer at five minutes intervals for 30 minutes and compared with the contralateral arm as reference using pin brick by a 22-gauge hypodermic needle at the following areas, the thenar eminence innervated by median nerve, the hypothenar region innervated by the ulnar nerve, the dorsum of the hand innervated by the radial nerve, the lateral aspect of the forearm innervated by the musculocutaneous nerve and the area over the insertion of the deltoid muscle for the Axillary nerve. The sensory block was assessed by a verbal rating scale from 100% (normal sensation) to 0% (no sensation). Onset of sensory block was defined as the time from last injection to complete loss of sensation in each of the major peripheral nerve distributions (ulnar, radial, medial, and musculocutaneous).

The motor block was evaluated using forearm flexion for the musculocutaneous, wrist extension for the radial nerve, thumb and index finger opposition for the median nerve and thumb and little finger opposition for the ulnar nerve. The muscle power was compared in relation to the contralateral side. Three point scale for motor function was used (0 = normal motor function, 1 = reduced motor strength but able to move fingers, and 2 = complete motor block). Onset of motor block was defined as the time from last injection to the inability of the patient to move the fingers or raise the hand.

Readiness for surgery was defined by time from last injection till complete sensory and motor block without need for infiltration of local anesthetics, administration of analgesics for pain in the surgical field, or general anesthesia. Patient surgeon satisfaction was detected (the patient and the surgeon were satisfied or not). In the case of block failure of any nerve distributions, the patients were excluded from the study. The withdrawn cases were replaced by new patients.

Intraoperatively, quality of the block was assessed according to muscle relaxation, need for sedation, need for analgesia, patient and surgeon satisfaction and hemodynamic changes including heart rate and mean arterial pressure. Hemodynamic changes were recorded every 5 minutes for the first 15 minutes and the every 10 minutes till the end of surgery. Intraoperatively, if the patient felt pain or anxiety or if the heart rate or mean arterial blood pressure were increased, the patient received 1mg midazolam for anxiety and fentanyl 0.5 µg/kg for pain intravenously and the total dose of the received midazolam and fentanyl were calculated.

Duration of sensory block defined as the time between onset of block and return of pin prick response, duration of motor block defined as the time between onset of block till return of complete muscle power and duration of analgesia defined as the time interval between the onset of complete sensory block and the time for request for the first rescue analgesic were evaluated.

At the end of surgery, the patients were transferred to recovery room, and they were monitored for any complications and discharged with an Aldert score ≥ 9. Postoperatively, all groups received 1 gram paracetamol intravenously every 12 hours.

The Visual Analog Scale (VAS) was typically a 10-cm line anchored 0=no pain and 10=worst possible pain) was evaluated at PACU, 2,4,6,8,10,12,14,16,18,20,22 and 24 hours from end of surgery. VAS; Patients with VAS ≥ 4 received rescue analgesia in the form of morphine 0.1 mg/kg IV.

Postoperatively, the time to first rescue analgesia and the total dose of analgesia consumed in the first 24 hours in the three groups were calculated. Also, postoperatively, hemodynamic changes including heart rate and mean arterial blood pressure were evaluated for every hour for first four hours then every four hours till 24 hours.

2.1 Statistical Analysis

The sample size calculation was performed using G*Power (Kiel University, Kiel Germany) software version 3.1.9.2. The calculated sample size was (23) in each group based on the following consideration: 0.05 α error (two-sided) and 0.05 β error (Power of the study 95%). Group's ratio 1:1. Assumption that adding morphine or hyaluronidase might increase the duration of analgesia by about 25% compared with local anesthetic alone. The sample size was increased to 25 per group for dropouts.

Parametric variables (e.g., HR) were expressed as mean and standard deviation (SD). Comparison within the same group was done by repeated measures ANOVA test, while comparison among the three groups was done by F test with post hoc (LSD) test. Non-parametric variables (e.g., VAS) were expressed as median and interquartile range (IQR). Comparison within the same group was done by Friedman test with post hoc wilcoxon signed-rank test, while comparison among the three groups was done by Kruskal-Wallis test with Mann–Whitney (U) test. Categorial variables (e.g., sex) were expressed as frequency and percentage and were statistically analyzed by Chi-square test. P value ≤ 0.05 was considered statistically significant.

3. RESULTS

In this study, 101 patients were assessed for eligibility, 17 patients didn't meet the criteria and 9 patients refused to participate in the study. The remaining 75 patients were randomly allocated into three groups (25 patients in each); all patients were followed-up and analyzed statistically (Fig. 1).

Both groups were comparable in demo-graphic data (age, weight and gender), ASA physical status and duration of surgery (Table 1).

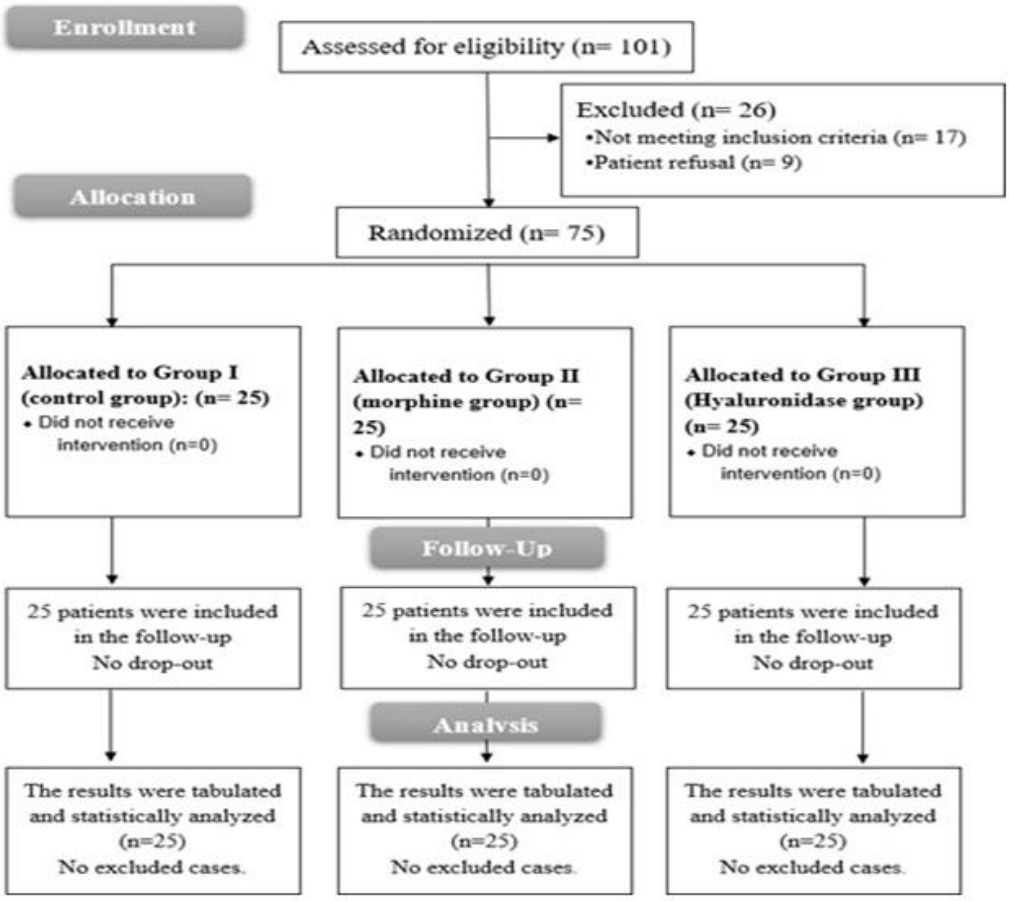

Fig. 1. Patient flowchart of the three groups

Table 1. Patients' characteristics among the three groups.

		Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value
Age(years)	Mean ± SD	40.6 ± 13.71	38.16 ± 12.67	42.24 ± 12.55	0.552
	Range	18-60	18-58	20-60	
Sex	Male	13 (52%)	18 (72%)	17 (68%)	
	Female	12 (48%)	7 (28%)	8 (32%)	0.297
BMI (kg/m^2)	Mean ± SD	26.57 ± 4.48	26.26 ± 5.20	28.37 ± 4.29	0.239
	Range	19.5-34.6	18-38.3	20.5-37.3	
ASA physical status	I	18 (72%)	20 (80%)	19 (76%)	
	II	7 (28%)	5 (20%)	6 (24%)	0.297
Duration of surgery (minute)	Mean ± SD	74.8 ± 9.74	77.6 ± 11.50	76.2 ± 10.03	
	Range	60-90	60-90	60-90	0.652
Type of surgery	Fracture ulna	4 (16%)	6 (24%)	5 (20%)	0.622
	Fracture radius	6 (24%)	9 (36%)	4 (16%)	
	Tendon repair of forearm	8 (32%)	4 (16%)	7 (28%)	
	Tendon repair of hand	7 (28%)	6 (24%)	9 (36%)	

BMI; body mass index. SD; stander deviation.

The mean onset of sensory block in group III was significantly shorter (10.08 ± 1.41 minutes) compared to either group I (14.96 ± 2.07 minutes) or group II (12.4 ± 1.72 minutes) (P < 0.001). The mean onset of motor block in group III was significantly shorter (14.24 ± 2.06 minutes) compared to either group I (19.44 ± 2.28 minutes) or group II (16.76 ± 1.82 minutes) (P < 0.001). Group II also showed a significant shorter mean onset of motor and sensory block than group I.

The mean duration of sensory block in group II was significantly longer (12.17 ± 1.69 hours) compared to either group I (7.17 ± 1.73 hours) or group III (7.32 ± 1.67 hours) (P < 0.001). Comparison of duration of sensory block in group I to group III was insignificant as (P = 0.953 and 0.989 respectively). The mean duration of motor block in group II was significantly longer (11.32 ± 1.78 hours) compared to either group I (6.38 ± 1.72 hours) or group III (6.45 ± 1.7 hours) (P < 0.001).

Intraoperative heart rate and mean arterial blood pressure were insignificantly different among the three groups at 5,10,15,25,35,45,55,65 and 75 minutes (P values > 0.05). At 8, 16 and 24 hours, postoperative heart rate was significantly increased in group I than group II (P1 = 0.032, <0.001 and 0.001 respectively), while significantly decreased in group II than group III (P3 = 0.005, 0.001 and0.040 respectively) and there was insignificant difference between group I and group III (P2 = 0.482, 0.678 and 0.129 respectively). At 16 and 24 hours, postoperative mean arterial blood pressure was significantly increased in group I than group II (P1 = 0.003 and 0.005 respectively). And it was significantly decreased in group II than group III (P3 = 0.043), while there was insignificant difference between group I and group III (P2 = 0.301 and 0.057 respectively) (Fig. 2-5).

At 18, 20 and 24 hours, VAS was significantly increased in group I than group II (P1 = 0.003, 0.009, <0.001, <0.001, <0.001 respectively), while it decreased in group II than group III (P3 = 0.009, 0.006 and 0.002 respectively), while it significantly decreased in group I than group III (P2 = 0.002, 0.002 and 0.005 respectively) (Fig. 6).

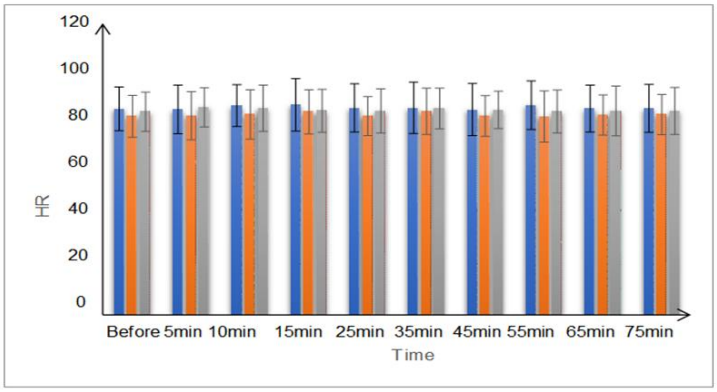

Fig. 2. Intraoperative heart rate among the three groups

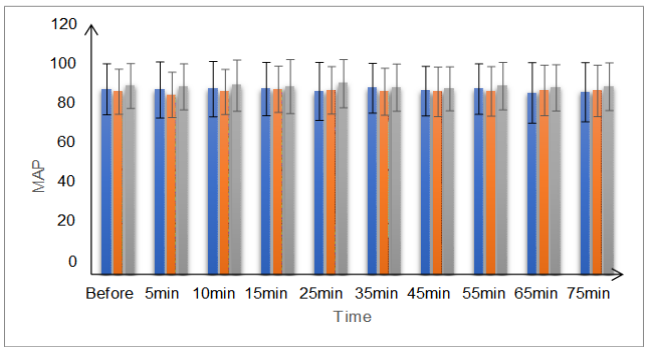

Fig. 3. Intraoperative mean arterial blood pressure among the three groups

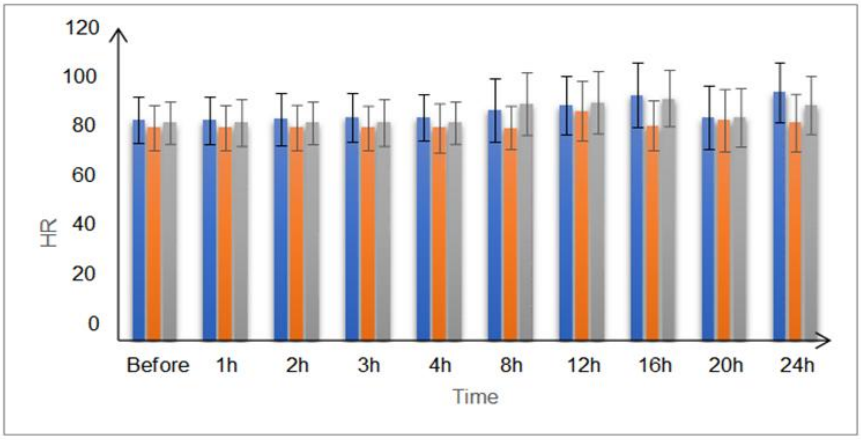

Fig. 4. Postoperative heart rate among the three group

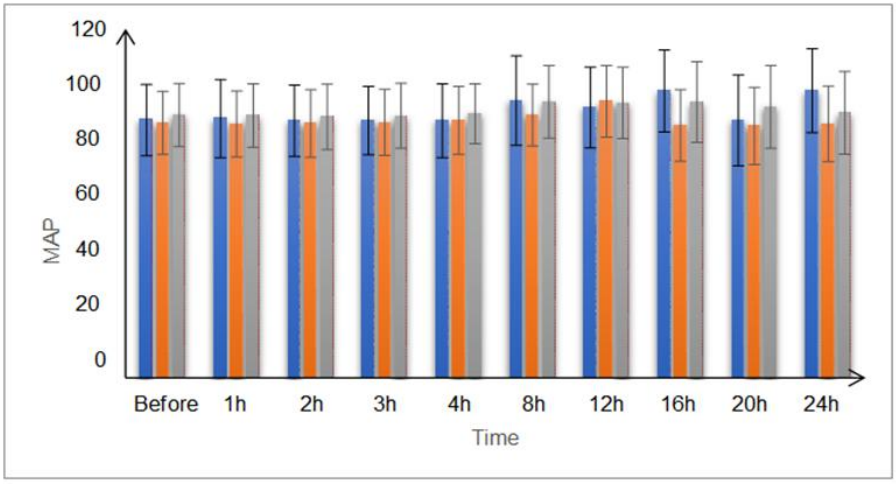

Fig. 5. Postoperative mean arterial blood pressure among the three groups

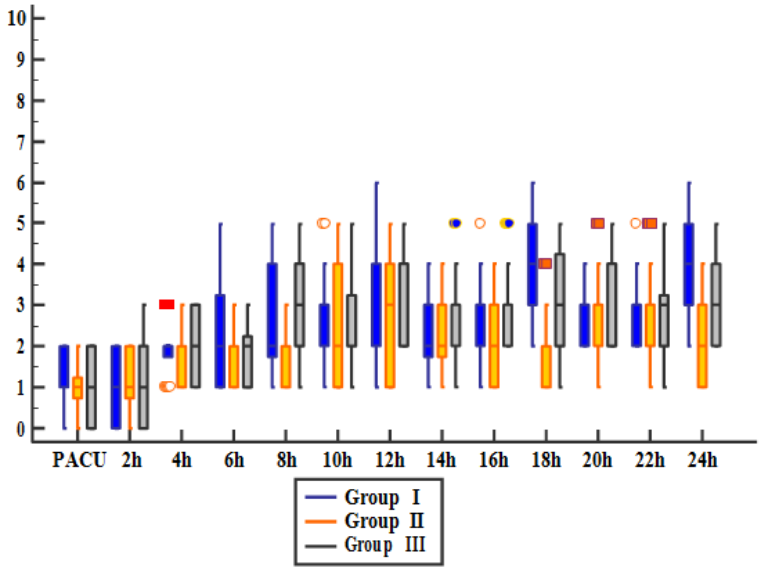

Fig. 6. Visual analogue scale (VAS) among the three groups

Time of first rescue analgesia was significantly prolonged in group II (10-14 hours) compared to both group I (5-8 hours) and group III (5-8 hours), (P1 <0.001 and P3 <0.001). Total analgesic consumption (morphine) was significantly lower in group II (7-27 mg) compared to both group I (12-32 mg) and group III (14- 36 mg), (P1 <0.001 and P3 <0.001).

Post-operative nausea and vomiting (PONV) occurred in 3 (12%) patients in group I, 1 (4%) patients in group II and 2 (8%) patients in group III. PONV was insignificantly different among the three groups (p=0.581). Bradycardia, hypotension, respiratory depression, pneumothorax, hematoma, numbness, paraesthesia and local anaesthetic systemic toxicity (LAST) didn't occur in any patient.

4. DISCUSSION

There is an advantage in reducing the time to reach complete sensory block as the turnover time between operations can be reduced and operation rooms can be used more efficiently, especially in circumstances in which there is no special area to perform a block. If onset of sensory block is prolonged, supraclavicular block may be harder to justify than general anaesthesia, especially for day-case surgeries [10].

In current study, onset of the sensory block and motor block was significantly shorter in the hyaluronidase group than other two groups and in morphine group than control group. While duration of the sensory block and motor block was significantly prolonged in morphine group than hyaluronidase group & control group.

In accordance with the present study, Kawthar Mohamed and Khaled Abdelrahman in 2019 concluded that onset and duration of touch and pain block was faster in morphine group. Morphine provides better postoperative analgesia when injected with local anaesthetics in ultrasound guided axillary brachial plexus block without an increase in the frequency of complications. But against the present study, the duration of motor block showed no change between the two groups [11].

Similar to the present results, a study done by Bazin et al. [12] concluded that the addition of morphine to a local anaesthetic mixture lengthens the duration of analgesia.

In agreement with the present study, Saryazdi et al. [13] found that addition of morphine or pethidine to lidocaine is superior to other opioids (i.e. fentanyl and buprenorphine) due to better quality and quantity of motor blockade and faster onset of the block in the upper extremity surgeries performed under axillary brachial plexus block.

Another study by Viel et al. [14] concluded that buprenorphine injection into the brachial plexus sheath is better than morphine to control postoperative pain after upper limb surgery.

Against our study, a study by Racz et al. [15] concluded that addition of morphine to the local anaesthetic solution for the axillary block didn't shorten the onset time of the block, improve the quality of postoperative pain relief, or provide longer lasting analgesia than that obtained with intramuscular morphine.

In disagreement with the present study, Wang et al. [16] concluded that dexmedetomidine can provide superior analgesia for interscalene brachial plexus block in adjunct to 0.5% ropivacaine when compared with morphine. As an adjuvant, morphine may have few significant benefits in peripheral nerve block.

In a harmony with the present study, Kamal Hakim et al. [17] concluded that the use of hyaluronidase as an adjuvant to the local anaesthetic reduces the time to reach complete sensory block of ultrasound-guided supraclavicular brachial plexus blocks and therefore shortens the total anaesthetic time before operation. Although it also reduces the block duration, hyaluronidase had only a little effect on the total analgesic duration and on the consumption of postoperative analgesics.

In contrast with the present study, Said et al. [18] found that addition of hyaluronidase to local anaesthetic during supraclavicular brachial plexus block didn't increase the speed of onset of anaesthesia, but it produced a significant reduction in the duration of anaesthesia.

Against with the present study, Krediet et al. [19] found that addition of hyaluronidase to local anaesthetic had no measurable effects on a motor or sensory block of single injection axillary brachial plexus block.

In a harmony with our study, according to Adams et al. [20], hyaluronidase was commonly used as an adjuvant in ophthalmic surgery to fasten the onset time of the ocular block and increase the success rate.

Nicoll et al. [20] found that adding hyaluronidase 15 IU/mL to a mixture of bupivacaine and lidocaine in retrobulbar anesthesia significantly improved the motor block.

In the present study, VAS started to increase at 6 hours in control group, and at 10 hours in morphine group and at 8 hours in hyaluronidase group. VAS was significantly different between the three groups at 4, 12, 18, 20 and 24 hours.

VAS was significantly increased in control group compared to either morphine group or hyaluronidase group at 18, 20 and 24 hours. VAS was significantly decreased in morphine group than hyaluronidase group.

In line with the present study, Kawthar Mohamed et al. [21] in 2019 found that VAS at 8 hr showed no significant change between placebo group and morphine group. VAS at 12, 18 and 24 hours was significantly lower in morphine group than placebo group.

Our study was supported by Salah et al. [22] in 2017 who concluded that addition of hyalourindase to bupivacaine for transversus abdominis plane (TAP) block resulted in significant reduction in VAS pain score over the post- operative 24hours and reduction of post-operative morphine requirements.

This study was supported by a study of Chaudhari et al. [23] in which VAS scores were statistically lower in the hyaluronidase group at 2 and 6 hours postoperatively in inguinal hernia block.

In the present study, time to first rescue analgesia was significantly prolonged in morphine group than control group and hyaluronidase group while insignificant difference between control group and hyaluronidase group was found.

In a harmony with the present study, Bourke et al. [24] concluded that morphine group required approximately half of analgesic dose than the control group during ultrasound guided axillary block.

In line with the present study, Krohn et al. [25] found that the frequency of complications in cataract surgery was less when hyaluronidase was added to the local anaesthetic solution.

Hyaluronidase was successfully used as an adjuvant to local anaesthetics in ocular blocks where in it could shorten block onset time and improve quality of anaesthesia with minimal reported side effects [26].

Steven et al. [27] found that hyaluronidase usage in regional anaesthesia revealed great variabilty in doses and methodology; this indicated high success rate and safety of hyaluronidase use. Limitations of the study are the relatively small sample size and being a single centre study.

5. CONCLUSION

Addition of morphine or hyaluronidase to local anaesthetic in the ultrasound guided supraclavicular brachial plexus block resulted in improving the quality of anaesthesia with shorter onset in the hyaluronidase group and longer duration in the morphine group.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL AND CONSENT

The study was approval by ethical committees. An informed consent was obtained from all participants; supraclavicular block and the visual analogue scale were explained to the patients preoperatively.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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