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Original Article

Anaesthesia Section

The Effect of Hyaluronidase as an Adjuvant to Local Anaesthetics in Peripheral Nerve Stimulator-guided Supraclavicular Brachial Plexus Block: A Randomised Controlled Study

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ABSTRACT

Introduction: For upper limb procedures using the supraclavicular approach to brachial plexus block, various adjuncts to Local Anaesthetics (LA) have been employed to improve the quality and duration of anaesthesia and postoperative analgesia without leading to any adverse side-effects or prolonging the period of motor block. Hyaluronidase is an enzyme used with other drugs to accelerate their dispersion and distribution. It catalyses the hydrolysis of a component of the extracellular matrix, hyaluronan, thereby lowering its viscosity and improving tissue permeability.

Aim: To evaluate the sensory and motor blockade resulting from the addition of hyaluronidase as an adjuvant to LA in Peripheral Nerve Stimulator (PNS)-guided Supraclavicular Brachial Plexus Block (SBPB).

Materials and Methods: This prospective, comparative, double-blinded, randomised controlled study was conducted in a Department of Anaesthesiology S.B.K Shah Medical Institute and Research Centre, Vadodara, Gujarat, India at a tertiary care hospital on 72 patients undergoing elective upper limb surgeries under PNS-guided SBPB over 18 months from November 2022 to August 2024. Group B (n=36) received inj. bupivacaine (0.5%) 13 mL, inj. lignocaine with adrenaline (2%) (1:200,000) 13 mL, and inj. normal saline (0.9%) 4 mL, for a total of 30 mL, and Group H (n=36) received inj. bupivacaine (0.5%) 10 mL, inj. lignocaine with adrenaline (2%) (1:200,000) 10 mL, inj. hyaluronidase (900 IU) 6 mL, and inj. normal saline (0.9%) 4 mL, for a total of 30 mL. Sensory and motor blockade and rescue analgesia were recorded at 0, 1, 3, 5, 7, and 10 hours. Categorical variables were analysed using the Chi-square test. To analyse continuous variables, the student's t-test was used. The p-value of less than 0.05 was deemed statistically significant.

Results: The onset time of sensory and motor block was earlier with Group H (2.36±0.25 minutes and 4.2±0.29 minutes) than with Group B (4.54±0.25 minutes and 6.51±0.29 minutes), respectively ($p<0.05$). The sensory and motor block lasted longer in Group B (278.8±7 minutes and 266.8±6.78 minutes) than in Group H (263.2±7 minutes and 246.3±6.78 minutes) respectively, $p<0.05$. The duration of analgesia was longer with Group B (240.8±7.84 minutes) compared to Group H (220±7.84 minutes) $p<0.05$. No major adverse effects were observed.

Conclusion: Addition of hyaluronidase to a lower volume of LA results in rapid onset of the block with minimal side-effects.

Keywords: Bupivacaine, Glycosidases, Nerve block, Upper extremity

INTRODUCTION

The supraclavicular approach of the brachial plexus block has many advantages over other approaches for upper limb surgeries in Orthopaedics. The supraclavicular block is conducted at the trunk level, where the brachial plexus is most densely packed. This approach targets the middle portion of the brachial plexus [1,2]. For most clinical cases, modern LA are both effective and safe; nonetheless, the hunt for drugs with an earlier mode of block onset and longer duration of action is ongoing [3]. A range of adjuncts to LAs for brachial plexus block have been used to increase both the quality and duration of anaesthesia and postoperative analgesia while avoiding adverse effects and extending the length of motor block. [3] Magnesium sulfate [4], hyaluronidase [1], sodium bicarbonate [3], potassium chloride [5], and opioids [6] are a few examples.

The PNS-guided SBPB is a popular regional anaesthetic upper limb surgical procedure with multiple applications. It helps to locate nerves to be blocked by regional anaesthesia [7]. In addition to providing superior analgesia and extending regional blockade, brachial plexus nerve blocks with additives for procedures of the upper limb significantly reduce the need for analgesics throughout the recovery period and prevent the negative effects of general anaesthesia [7].

Hyaluronidase acts by catalysing the hydrolysis of a component of the extracellular matrix, hyaluronan. It reduces the viscosity of hyaluronan, enhancing tissue permeability; consequently, it is utilised in combination with other medications to accelerate their dispersion and administration [1].

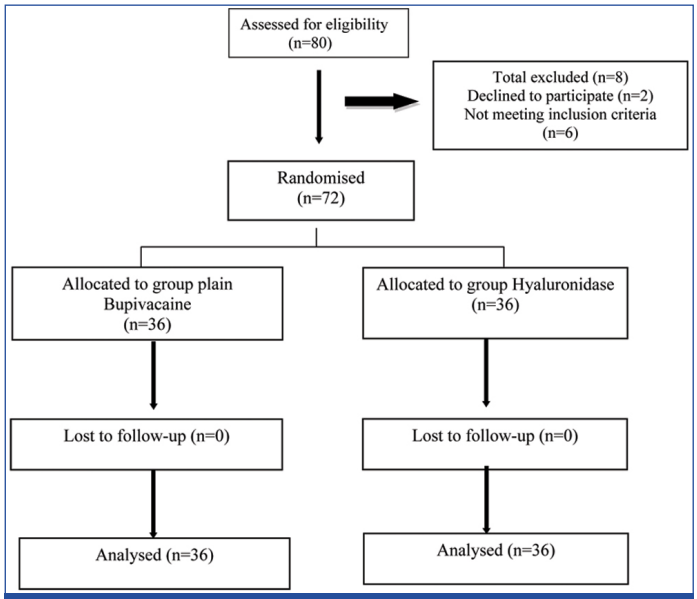
Given its recent popularity and safety profile in other areas, hyaluronidase has frequently been used in conjunction with insulin to treat diabetes, beta interferons to treat multiple sclerosis, biotherapeutics to treat rheumatoid arthritis, immunoglobulin replacement therapy for primary immunodeficiency disorders, and monoclonal antibodies to treat cancer [8]. Hyaluronidase has also gained a significant place as an adjunct in eye blocks under local anaesthesia for ophthalmic procedures [8]. However, its worth as a LA adjuvant in peripheral nerve blockades has yet to be established. The current study uses hyaluronidase as an adjuvant to evaluate its efficacy along with the mixture of LA in PNS-guided SBPB and assess the quality of the block for patients undergoing elective upper limb surgeries with the primary outcome being the onset and duration of sensory and motor blockade, duration of analgesia, and the secondary outcome being hemodynamic changes during the procedure.

MATERIALS AND METHODS

This prospective, comparative, double-blinded, randomised clinical study was conducted in the Department of Anaesthesiology S.B.K Shah Medical Institute and Research Centre, Vadodara, Gujarat, India at a tertiary care hospital for elective upper limb surgeries under PNS-guided SBPB from November 2022 to August 2024. Approval was obtained from the Institutional Ethics Committee (SVIEC/ON/MEDI/BNPG21/NOV/22/104).

Inclusion and Exclusion criteria: Patients willing to sign the written informed consent form, ASA grade I and II of either gender aged 18-55 years, and undergoing elective upper-limb surgeries were included. Refusal to participate in the study, local site infection, known allergy to the drug, coagulation disorder, or being on anticoagulant therapy, as well as patients with any morbid systemic diseases, were excluded from the study.

Entire procedure is shown Consodilated Standards of Reporting Trails (CONSORT) flow diagram [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.

Sample size calculation: The sample size and power were calculated with the help of a sample size calculator using the formula [9].

$$n_A = \kappa n_B \text{ and } n_B = \left(\frac{p_A(1-p_A)}{\kappa} + p_B(1-p_B)\right)\left(\frac{z_{1-\alpha/2} + z_{1-\beta}}{p_A - p_B}\right)^2$$

$$1-\beta = \Phi\left(z - z_{1-\alpha/2}\right) + \Phi\left(-z - z_{1-\alpha/2}\right), \quad z = \frac{p_A - p_B}{\sqrt{\frac{p_A(1-p_A)}{n_A} + \frac{p_B(1-p_B)}{n_B}}}$$

Where,

K=nA/nBκ=nA/nB is the matching ratio

ΦΦ is the standard normal distribution function

Φ-1Φ-1 is the standard normal quantile function

Aα is Type I error

Bβ is Type II error, meaning 1-β1-β is power

Considering a 10% difference and a significance level of 5%, the sample size was calculated to be a total of 72, with 36 in each group. The sample size was increased to 40 in each group to accommodate a 10% dropout rate.

Study Procedure

The objective, nature, and methodology of the study were thoroughly explained to each patient in a language they could comprehend. Patients were allocated randomly into two groups by the chit method (72 chits of either Group B or Group H). Anaesthesiologists involved in data collection and patient care were blinded to the drug of the study solution because it was made by an anaesthesiologist who was not involved in the study.

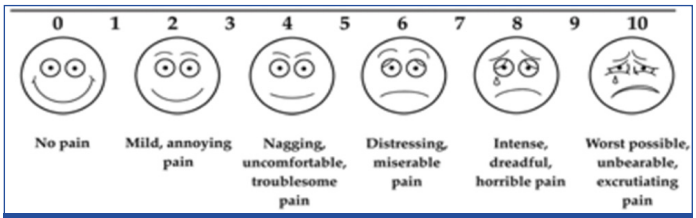
Prior to surgery, all patients were kept nil by mouth for eight hours. The patients were moved to the operating room on the day of the operation. As soon as the patient entered the operating room, a multiparameter monitor was connected that measured their Heart Rate (HR), continuously recorded Electrocardiogram (ECG), Oxygen Saturation (SpO_2), and non invasive readings of their Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP). Every patient received a premedication injection of 0.2 mg of glycopyrrolate, 4 mg of ondansetron, 40 mg of pantoprazole, and 1 mg of midazolam intravenously through an 18 G vein flow with Ringer's lactate according to fluid deficit. With the patient in a supine position and the bolster under the shoulder, the neck was turned to the opposite side. The arm that would be anaesthetised was adducted. Taking all antiseptic and aseptic measures, lateral to the subclavian artery and 1 to 1.5 cm above the clavicular midpoint, a block was given using a 24 G x 1.5-inch Stimuplex needle with a PNS. The PNS was started with an intensity of 3.0 mA at a frequency of 1 Hertz to obtain a defined response (muscle twitch of two fingers at an intensity of 0.5 mA) and to locate the peripheral nerve; current was gradually reduced to a target of 0.2 mA when the response stopped.

Group B: Inj. bupivacaine 0.5% 13 mL+inj. lignocaine with adrenaline 2% (1:200,000) 13 mL+inj. sterile normal saline 0.9% 4 mL-total 30 mL.

Group H: Inj. bupivacaine 0.5% 10 mL+inj. lignocaine with adrenaline 2% (1:200,000) 10 mL+inj. hyaluronidase 900 IU 6 mL+inj. sterile normal saline 0.9% 4 ml-total 30 mL [1,10,11].

The anaesthesiologist not related to the study administered the drug after negative aspiration. A total drug volume of 30 mL was given in 5 mL incremental doses. For a minute, a quick massage was given to aid in uniform drug distribution. Motor block was assessed with Bromage's three-point scale [4], i.e., Grade 0- Complete flexion and extension of the elbow, wrist, and fingers; Grade 1- Reduced motor power, limited to moving the wrist and/or fingers; and Grade 2- Total motor blockage, resulting in finger immobility. Sensory block was assessed with the pinprick method [12], i.e., Grade 0- Normal sensation; Grade 1- Impaired sensation; and Grade 2- Loss of sensation.

Pain was assessed postoperatively using a Visual Analogue Score (VAS) [Table/Fig-2] [13]. Rescue analgesia was given when the VAS score was ≥4. Sensory and motor blockade were assessed, and rescue analgesia was recorded at 0, 1, 3, 5, 7, and 10 hours. Side-effects or adverse effects were recorded.



[Table/Fig-2]: Visual Analogue Scale (VAS) [13].

The time of motor block onset was calculated as the time period in minutes from time zero until the motor block appeared, resulting in a Bromage score of 2. The duration of motor block was calculated as the time in minutes between the total complete motor block and the time when the Bromage score equaled 0 in the postoperative phase. The pinprick response on the areas of all four upper-limb nerves (radial, ulnar, median, and musculocutaneous) was used to assess the onset of sensory block. The total sensory block duration was observed from complete loss of sensation until the patient started to feel sensation on the fingertips. Duration of analgesia was measured from the time of drug injection till VAS score of ≥4.

STATISTICAL ANALYSIS

The data were analysed using Microsoft (MS) Excel version 16.89.1. Numerical variables were represented by mean and Standard Deviation (SD), while categorical data were represented by frequency and percentage. To compare groups based on numerical variables, the unpaired Student t-test was employed. For categorical variables, the Chi-square test was employed. A statistically significant difference was defined as one with a significance level ($p<0.05$).

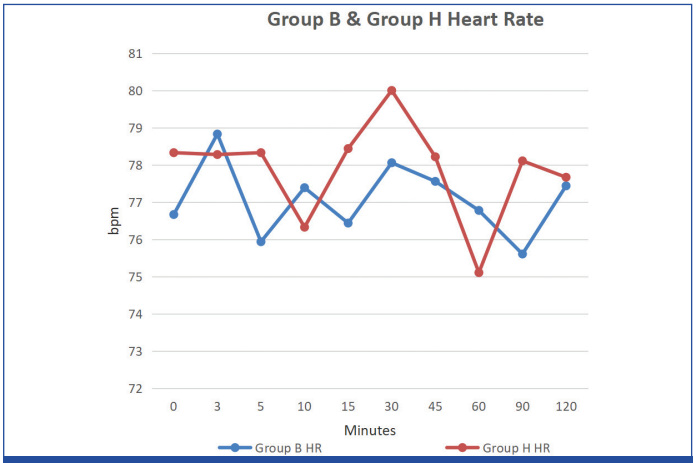
RESULTS

Both groups had comparable demographic data in terms of age, weight, gender, and ASA grading [Table/Fig-3], with $p>0.05$.

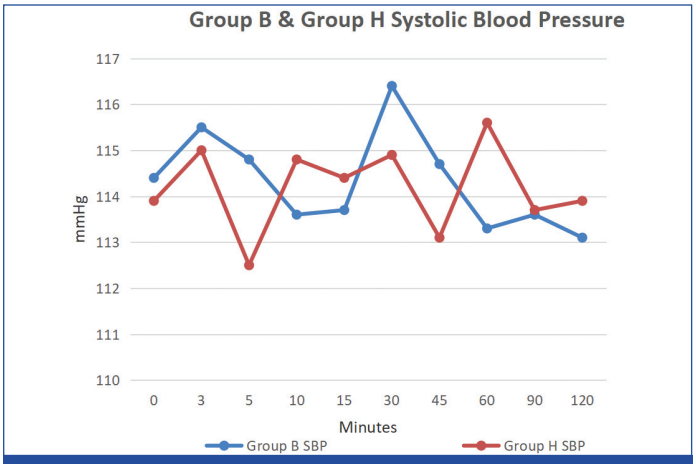
Parameters	Group B	Group H	p-value*
	Mean±SD		
Age (years)	38.86±3.55	36.78±3.55	0.55 (NS)
Weight (kg)	61.53±2.05	65.06±2.06	0.09 (NS)
Gender	n (%)	n (%)	
Male	18 (50%)	23 (63.89%)	0.59 (NS)
Female	18 (50%)	13 (36%)	
ASA grade	**n (%)**	**n (%)**	
I	21 (58.33%)	16 (44.44%)	0.23 (NS)
II	15 (41.66%)	(55.55%)	

[Table/Fig-3]: Results of demographic parameters.
Chi-square test; Used for categorical variables {Gender and American Soceity of Anaesthesiologist (ASA) Grade}; Student's t-test: Used for a continuous variable (Age). Statistical *p>0.05 (NS) Not significant.

The intraoperative haemodynamics remained stable in both groups ($p>0.05$) has been depicated in [Table/Fig 4-6].

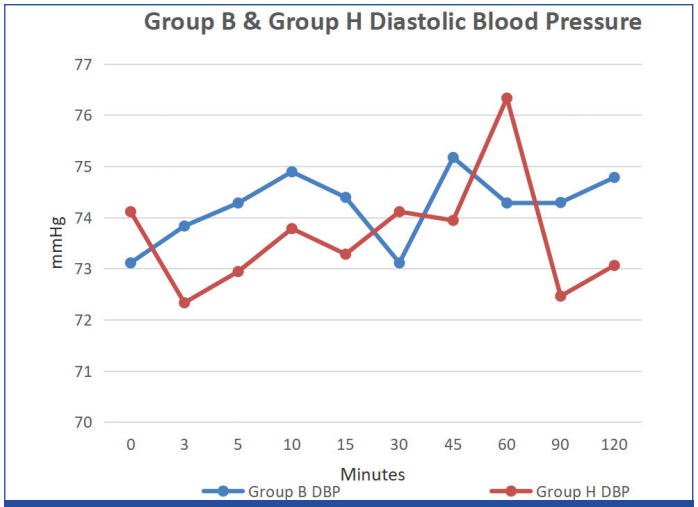


[Table/Fig-4]: Comparison of Heart Rate (HR) at different time intervals.



[Table/Fig-5]: Comparison of Systolic Blood Pressure (SBP) at different time intervals.

The onset of sensory block was faster in Group H compared to Group B ($p<0.0001$). The duration of sensory and motor block and rescue analgesia were longer in Group B than in Group H



[Table/Fig-6]: Comparison of diastolic blood pressure at different time intervals.

($p<0.05$). [Table/Fig-7,8] show that at five hours after giving the block in groups B and H, 100% of patients achieved a VAS score of ≥4, indicating that both groups were comparable. There was no significant difference in the side-effects noted in either group ($p=0.292$) [Table/Fig-9].

Parameters	Group B	Group H	p-value*
	Mean±SD		
Onset time of sensory block (minutes)†	4.54±0.25	2.36±0.25	<0.0001 (S)
Onset time of motor block (minutes)†	6.51±0.29	4.20±0.29	<0.0001 (S)
Duration of surgery (minutes)	84.31±7.00	72.36±7.00	0.09
Duration of effective sensory block (minutes)†	278.8±7.00	263.2±7.00	0.029 (S)
Duration of effective motor block (minutes)†	266.8±6.78	246.3±6.78	0.003 (S)
Time of first rescue analgesia (minutes)†	240.8±7.84	220.0±7.84	0.009 (S)

[Table/Fig-7]: Comparison of onset, duration of sensory and motor block and time to first rescue analgesia and duration of surgery.
Student t-test applied, where †p-value <0.05 considered significant- S

Time (hours)	0 n (%)	1 n (%)	3 n (%)	5 n (%)	7 n (%)	10 n (%)
Group B	0	0	0	36 (100%)	0	0
Group H	0	0	0	36 (100%)	0	0

[Table/Fig-8]: VAS ≥4 at different time intervals.
Chi-square test; Used for categorical variable

Side-effects	Group B		Group H		p-value
	n	%	n	%	
Nausea	2	40%	3	60%	0.292
Vomiting	1	33.33%	2	66.67%	

[Table/Fig-9]: Side-effects observed in both the groups.
Chi-square test; Used for categorical variables, p>0.05 considered (NS) Not significant

DISCUSSION

The designated endpoints of the current study were to analyse the efficacy of combining hyaluronidase and bupivacaine in SBPB and evaluate the overall quality of the block for patients undergoing elective upper limb surgeries. The study's results unequivocally showed that the use of hyaluronidase as an adjuvant was effective in improving block quality, thus promoting patient and surgeon compliance by contributing to early block onset and facilitating postoperative early mobilisation. This was achieved as a lesser volume of LAs was used, which helped the surgeon evaluate any potential neurovascular damage postsurgery and aided in the patient's recovery.

In the current study, patient characteristics such as age, gender, and weight were comparable in either group. The average duration of the surgery in both groups was also similar ($p>0.05$).

The study concluded that Group H with hyaluronidase and LAs had a significantly shorter onset of sensory and motor blockade compared to Group B. This could be attributed to the effect of hyaluronidase, which aids in faster drug dispersion and delivery by increasing tissue permeability. This result is supported by Mostafa TA et al., who evaluated the effect of hyaluronidase with different concentrations of bupivacaine in ultrasound-guided SBPB [10]. The time of onset for sensory and motor blockade in that study was delayed (10.3±2.3 and 13.7±3.3 minutes, respectively) compared to the current results (2.36±0.25 and 4.20±0.29 minutes, respectively). This difference can be attributed to the use of plain bupivacaine without lignocaine-adrenaline and a comparatively lesser dose of hyaluronidase (500 IU) used in the study population, which consisted of ASA grade III patients with chronic renal failure and end-stage disease. Hakim K and Ahmed M, supported the present results but showed a delayed onset comparatively due to the use of plain lignocaine (2%) without adrenaline, which could be one of the contributing factors [1]. Similarly, Elhussein AK et al., showed early onset with hyaluronidase (1000 IU) when compared to magnesium sulfate as an adjuvant along with bupivacaine without lignocaine-adrenaline [4].

The outcome of the block duration was significantly prolonged for Group B compared to Group H. Similar findings were observed by Mostafa TA et al., in their study, which used the same volume of drug, i.e., 30 ml of bupivacaine and hyaluronidase (1500 IU) [10]. Contrasting results regarding prolonged block duration were seen in studies conducted by Hakim K et al., Elsayed S et al., due to a higher volume of total drug used (40 mL), and by Koh WU et al., where ropivacaine was used along with 3000 IU of hyaluronidase [1,11,14].

The duration of analgesia, i.e., the time to first rescue analgesia in the current study, was prolonged for Group B compared to Group H. This result coincided with the study by Hakim K et al., where a similar drug volume and concentration (30 mL) were used [1]. Elsayed S et al., compared hyaluronidase with adrenaline along with the control group in 90 patients [11]. Koh WU et al., in the study compared hyaluronidase (3000 IU) + ropivacaine (0.5%) with plain ropivacaine (0.5%), but prolonged block duration was observed in all of these studies [14].

A VAS score ≥4 was observed at five hours in both groups, similar to the study results by Elmaghraby AE et al., where at eight hours, hyaluronidase (1500 IU) was used [6]. None of the other studies evaluated the time when the VAS score was ≥4; instead, they assessed the number of patients who needed postoperative rescue analgesia, with no significant results obtained in Mostafa TA et al., study [10].

No significant complications or side-effects related to the drug or block were encountered in either of the groups in the index study, similar to previous studies.

Limitation(s)

Only normotensive (ASA I and II) patients have been included, and the outcomes may not reflect the effectiveness and safety of hypertensive patients due to the use of adrenaline in LAs, in whom intraoperative haemodynamics are crucial.

CONCLUSION(S)

Hyaluronidase, as an adjuvant to a lower volume of LAs, causes a rapid onset of block with minimal side-effects. The duration of motor block is shorter with hyaluronidase compared to a higher volume of plain LAs, facilitating early assessment of limb movements for the surgeon following surgery to rule out any iatrogenic nerve injury.

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