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Original Article

Anaesthesia Section

Comparison of Soda Bicarbonate and Hyaluronidase as an Adjuvant to Bupivacaine in Supraclavicular Brachial Plexus Block: A Double Blinded Randomised Clinical Study

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ABSTRACT

Introduction: For upper limb surgeries, brachial plexus nerve blocks with additives offer efficient analgesia and prolonged regional block. Hyaluronidase is an enzyme, which catalyses the hyaluronan and lowers its viscosity, improving tissue permeability of Local Anaesthetics (LA) to accelerate their dispersion and distribution. Adjuvant sodium bicarbonate raises the pH of the LA, improving tourniquet tolerance, resulting in greater analgesia quality, early onset and longer duration of sensory and motor blockade.

Aim: The aim of this study was to compare the effects of soda bicarbonate and hyaluronidase as an adjuvant to bupivacaine in Supraclavicular Brachial Plexus Block (SBPB).

Materials and Methods: The present double blinded randomised clinical study was conducted in a tertiary care hospital on 40 patients undergoing elective upper limb surgeries under Peripheral Nerve Stimulator (PNS) guided - SBPB. In addition to inj. bupivacaine 0.5% 18 mL+inj. lignocaine with adrenaline 2% (1:200000) 10 mL, Group S (n=20) received inj. soda bicarbonate 7.5% w/v 1 mL and Group H (n=20) received inj. hyaluronidase 900IU 1 mL - a total 29 mL. The onset time, duration of sensory and motor blockade were recorded. Rescue analgesia was 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 taken to be statistically significant.

Results: The demographic data were comparable in both the groups. Time of sensory block in Group H was 2.1±0.8 minutes and in Group S was 2.7±0.4 minutes, $p<0.05$. The onset for motor block in both groups was comparable. Duration of sensory and motor blockade were 399.5±26.35 minutes; 376.25 ±26.60 minutes and 270.75±35.22 minutes; 251.75±34.23 minutes, while time of rescue analgesia was 354.00±26.98 and 223.00±41.75 minutes in Group S and Group H, respectively, $p<0.05$. VAS was comparable, but at five and seven hours 45%; 55% and 100%; 0% received rescue analgesia in Group S and Group H, respectively, $p<0.05$. No major adverse effects were noticed.

Conclusion: Addition of hyaluronidase as an adjuvant causes faster onset of block, with minimal/no side effects, earlier postoperative mobilisation in comparison to soda bicarbonate. Duration of analgesia is more with soda bicarbonate compared to hyaluronidase.

Keywords: Local anaesthetic, Peripheral nerve plexus block, Peripheral nerve stimulator, Polysaccharides, Upper limb surgery

INTRODUCTION

Brachial plexus block has become an integral part of regional anaesthesia, providing a precise and effective method of pain management for upper limb surgical procedures [1]. Compared to other methods of brachial plexus block, the SBPB has numerous benefits. Since the plexus is most compactly presented at the trunk level, this is where it is performed. Middle of the brachial plexus is blocked. Hence, for upper limb procedures, comprehensive and dependable anaesthesia is a result of this anatomic compactness [2-5]. Hence, SBPB is also known as the spinal anaesthesia of the upper extremity [6]. And it can be safely used as a substitute for general anaesthesia, even for American Society of Anaesthesiologists (ASA) grade 3 patients, for any upper limb surgeries, due to its advantage of rapid onset, dense anaesthesia, and prolonged postoperative analgesia [6].

For the majority of clinical applications, modern LAs are safe and effective enough; nonetheless, researchers are still looking for agents with a longer half-life and an early block onset. Many adjuncts to LAs for brachial plexus block have been developed to enhance the quality and duration of anaesthesia and postoperative analgesia without causing adverse effects or extending the duration of motor block. Magnesium sulphate, hyaluronidase, soda bicarbonate, clonidine, dexmedetomidine and opioids are few examples [2,7-9]. Hyaluronan, a component in the extracellular matrix, is hydrolysed by hyaluronidase, which is how it works. Tissue permeability is increased when hyaluronidase decreases hyaluronan's viscosity [2,10,11]. Adjuvant sodium bicarbonate raises the pH of the LA, improving tourniquet tolerance, resulting in greater analgesia quality, early onset of sensory and motor blockade, and longer duration of blockade and analgesia [12,13].

Studies in this field have highlighted the potential benefits of adjuvants like clonidine, dexamethasone, fentanyl, and midazolam [8,9]. Each of these studies has produced favourable results, proving the adjuvants' capacity to prolong block duration and improve the standard of postoperative pain management [1]. However, despite these advancements, a comprehensive comparative analysis between hyaluronidase and soda bicarbonate, is currently lacking. The main goal was to study the effectiveness of hyaluronidase and soda bicarbonate as adjuvants to the LA mixture in PNS-guided SBPB, specifically the time of rescue analgesia and the onset and duration of sensory and motor block. Monitoring

any adverse events was the secondary goal. The current study therefore sought to add to the body of knowledge by evaluating soda bicarbonate and hyaluronidase as adjuvants to bupivacaine in PNS guided SBPBs, with the intent that the findings would improve patient care.

MATERIALS AND METHODS

This double blinded randomised clinical study was conducted in Department of Anaesthesiology SBK Shah Medical Institute and Research Centre, Vadodara, Gujarat, India at a tertiary care hospital on 40 patients undergoing elective upper limb surgeries under SBPB-PNS guided over a period of six months from July 2023 to December 2023. Approval was obtained from the Institutional Ethical Committee (SVIEC/ON/MEDI/SRP/JULY/23/125).

Inclusion and Exclusion criteria: Patients willing to sign the written informed consent form, American Society of Anaesthesiologists (ASA) grade I and II, including both genders, aged between 18 to 55 years undergoing elective upper limb surgeries with successful SBPB 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.

Sample size calculation: The sample size for this randomised clinical study was determined based on detecting a 10% difference in the primary outcome measure (e.g., time to rescue analgesia) between the two groups, at a 5% level of significance and 80% power [12,13]. The sample size and power were calculated with the help of a sample size calculator using the formula [14].

$$n=\{2\times(Z\alpha/2+Z\beta)^2\times\sigma^2\}/\Delta^2$$

Where:

$Z\alpha/2=1.96$ (for 95% confidence level)

$Z\beta=0.84$ (for 80% power)

σ (standard deviation)=35 (assumed from previous similar studies) [13]

Δ (mean difference to detect)=30 (10% of approximate average time to rescue analgesia) [12].

Now plugging into the formula:

$n=\{2\times(1.96+0.84)^2\times35^2\}/30^2\approx21.3$ per group

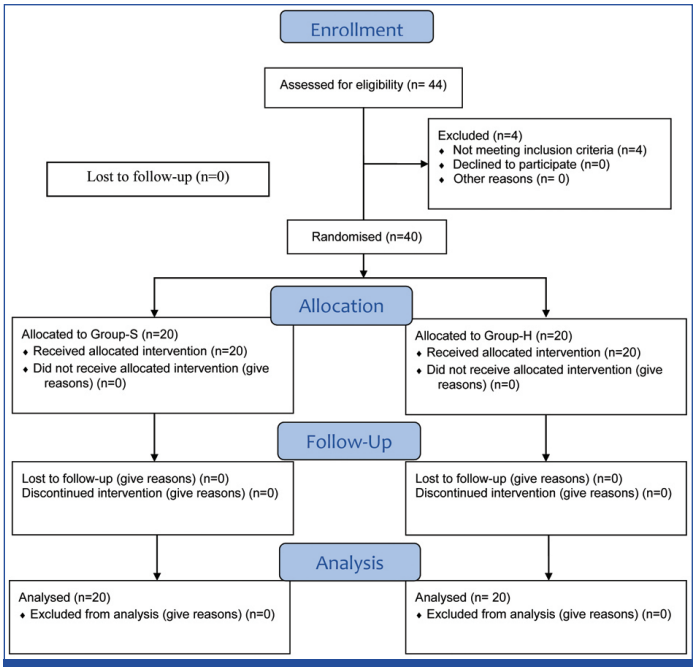
Thus, the minimum required sample size was approximately 22 patients per group.

Study Procedure

The objective, nature, and methodology of the study were all thoroughly explained to each patient in a language they could comprehend. 40 patients were allocated randomly into two groups (Group S and Group H) by computer generated randomisation in Microsoft Excel v.16.0.18623. The consultant anaesthesiologist not related to the study generated the block randomisation allocation sequence in form of 2:2 for equal distribution, enrolled the participants and assigned participants to the interventions. Investigator involved in data collection and patient care were blinded to the drug of the study. This was done to reduce the bias [Table/Fig-1].

1) **Group S:** Inj. bupivacaine 0.5% 18 mL+Inj. 2% lignocaine with adrenaline 1:200000 10 mL+Inj. soda bicarbonate 7.5% w/v 1 mL-total 29 mL [13].
2) **Group H:** Inj. bupivacaine 0.5% 18 mL+Inj. 2% lignocaine adrenaline 1:200000 10 mL+Inj. hyaluronidase 900IU 1 mL-total 29 mL [2,10,11].

The night before surgery, every patient was kept nil per oral for eight hours. On the day of the operation, the patients were transferred into the operating room. As soon as the patient entered the operating room, multipara monitor was connected that measured their Heart Rate (HR), continuous Electrocardiogram (ECG) recording,



[Table/Fig-1]: Consolidate standards of reporting trials flow chart.

Oxygen Saturation (SpO_2), and non-invasive measurements of their Systolic, Diastolic, and Mean Arterial Pressure (SBP, DBP, MAP). Every patient received premedication injection of 0.2 mg of glycopyrrolate, 4 mg of ondansetron, 40 mg of pantoprazole and 1 mg of midazolam intravenously through 18 G vein flow with Ringer's lactate according to fluid deficit. With the patient in supine position and the bolster under the shoulder, the neck was turned on opposite side. The arm to be anaesthetised was adducted. With all antiseptic and aseptic precautions, lateral to the subclavian artery and 1 to 1.5 cm above midpoint of the clavicle, block was given using 24G×1.5-inch stimuplex needle with PNS. The PNS was started with the intensity of 3.0 mA at frequency of 1 Hz to obtain a defined response (muscle twitch) to locate the peripheral nerve current is gradually reduced to a target of 0.2 to elicit any nerve involvement. The intensity of 0.5 mA, at which muscle twitches were visible, the anaesthesiologist not related to study administered the drug after negative aspiration. Total drug volume of 29 mL was given in 5 mL incremental doses. For one minute, a quick massage was given to aid in uniform drug distribution. Motor block was assessed with Bromage's scale [15]: Grade 0- Complete flexion and extension of the elbow, wrist, and finger; normal motor function; Grade 1- Reduced motor strength, limited to moving the wrist and/or fingers; Grade 2- Total motor blockage, resulting in finger immobility; and sensory block was assessed with pinprick method [16]: Grade 0- Normal sensation; Grade 1- Impaired sensation; Grade 2- Loss of sensation. Postoperative pain assessment was done by Visual Analogue Score (VAS) [17]. Rescue analgesia was given as inj. diclofenac 75 mg when the VAS score was ≥4. Side effects or adverse effects were recorded. Time of motor block onset was taken as the time interval in minutes from - Grade- 0 till motor block started to appear i.e., Bromage score ≥1.

The total motor block duration was the number of minutes from the start of the motor block to the point in the postoperative period when the Bromage score was measured as grade 0. The onset of sensory block was evaluated by the pin prick response on the areas of all four nerves of the upper limb. 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 v.16.0.18623. For categorical data representation frequency and percentage were

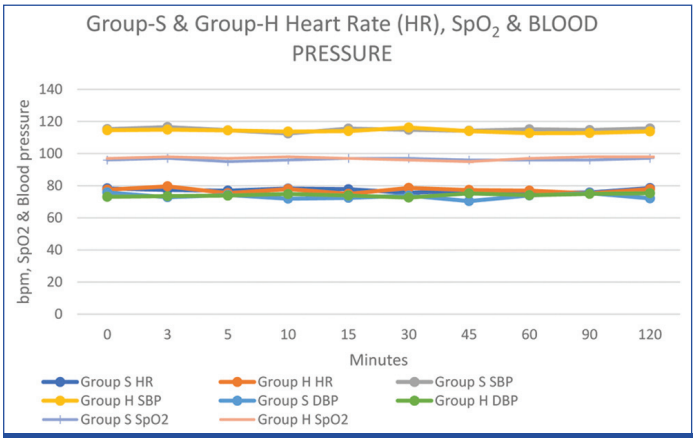
used while for mean and Standard Deviation (SD) representation, numerical variables have been used. To compare groups based on numerical variables, the unpaired student t-test was employed; for categorical variables, the Chi-square test was employed. A statistically significant difference was defined as one with a significant level ($p<0.05$).

RESULTS

Demographic data were comparable in both groups [Table/Fig-2]. Comparison of Heart Rate (HR), SpO_2 and blood pressure at different time intervals is shown in [Table/Fig-3].Sensory block onset was earlier in Group H compared to Group S ($p<0.05$). Duration of sensory and motor block and rescue analgesia were more in Group S than Group H ($p<0.05$) [Table/Fig-4].

Parameters	Group S Mean±SD	Group H Mean±SD	p-value
Age (years)	38.45±3.42	37.15±3.42	0.706
Weight (kg)	62.95±2.69	67.05±2.69	0.136
Gender n (%)			
Male	8 (40%)	13 (65%)	1.000
Female	12 (60%)	7 (35%)	
ASA			
I	12 (60%)	10 (50%)	1.000
II	8 (40%)	10 (50%)	

[Table/Fig-2]: Demographic parameters.
Chi-square test: Used for categorical variables (Gender and ASA grades), Student's t-test: Used for a continuous variable (Age), p>0.05=statistically not significant



[Table/Fig-3]: Showed that intraoperative haemodynamics remained stable in both the group.
p>0.05=Statistically not significant

Parameters	Group S Mean±SD	Group H Mean±SD	p-value
Onset time of sensory block (minutes)	2.74±0.46	2.17±0.89	0.017*
Onset time of motor block (minutes)	4.16±0.69	3.75±0.92	0.12
Duration of Surgery (minutes)	84.25±9.83	73.50±9.83	0.281
Duration of effective sensory block (minutes)	399.5±26.35	270.75±35.22	0.0001*
Duration of effective motor block (minutes)	376.25±26.60	251.75±34.23	0.0001*
Time of first rescue analgesia (minutes)	354.00±26.98	223.00±41.75	0.0001*

[Table/Fig-4]: Comparison of onset, duration of sensory and motor block and time to first rescue analgesia and duration of surgery.
(p<0.05=Statistically significant), *- Significant

[Table/Fig-5]: Shows that at five hours post block in Group H 100% of patients achieved VAS score of ≥4 while in Group S only 45%, suggesting longer duration of analgesia in Group S. Rescue analgesia was given as inj. diclofenac 75 mg when the VAS score was ≥4 to 9 patients of Group S and 20 patients of Group H at five hours. Side effects are shown in [Table/Fig-6].

Time	0 hour n (%)	1 hour n (%)	3 hours n (%)	5 hours n (%)	7 hours n (%)	10 hours n (%)
Group S	0	0	0	9 (45%)	11 (55%)	0
Group H	0	0	0	20 (100%)	0	0

[Table/Fig-5]: Visual Analogue Score (VAS) ≥4 at different time interval.

Side-effects	Group S	%	H	%	Total	p-value
Nausea	3	15	2	10	5	1.000
Vomiting	1	5	1	5	2	
Nil	16	80	17	85	33	
Total	20	100	20	100	40	

[Table/Fig-6]: Side-effects.

DISCUSSION

Now-a-days, brachial plexus blocks are frequently used for both elective and emergency upper limb surgeries. Various adjuvants are added to the LA solution in order to provide early anaesthesia onset with stable haemodynamics, increase the block duration, and promote postoperative analgesia [4,9,18]. In current study, we have compared the effect of adjuvants, hyaluronidase and soda bicarbonate in SBPB.

In this study, time of sensory block onset was early with Group H (2.1±0.8 minutes) than Group S (2.7±0.4 minutes). This result of soda bicarbonate is similar to study done by Patel DD et al., [13]. In contrast to present study, for onset of block with soda bicarbonate, the delayed onset was seen in Gupta S et al., and Ninan R et al., study due to use of lesser concentration of drugs 0.375% bupivacaine and 0.2 mL soda bicarbonate in relation to 0.5% bupivacaine and 1mL soda bicarbonate [12,19].

Current study showed that onset for motor block in both groups was comparable. And this result for soda bicarbonate coincided with the studies done by Gupta S et al., and Patel DD et al., [12,13]. Present study's result is in contrast with the study by Ninan R et al., due to lesser concentration of drugs, 0.375% bupivacaine and 0.2 mL soda bicarbonate in relation to 0.5% bupivacaine and 1 mL soda bicarbonate [19].

For hyaluronidase, the time of sensory and motor block onset does not coincide with any other studies as less volume or concentration of drug or different drug itself is used in all of them which can prolong the onset of block. In Hakim KY et al., study 900 IU hyaluronidase was used with 2% lignocaine without adrenaline, unlike current study [2]. In Mostafa TA et al., 1500IU hyaluronidase was used with 0.5% bupivacaine without lignocaine-adrenaline unlike present study [11]. Study by Elmaghraby AA et al., used 20mL of total volume without lignocaine-adrenaline unlike present study with 29mL and with lignocaine-adrenaline use [20].

Intraoperative haemodynamics remained stable throughout the study in both the groups. This study result has duration of sensory and motor block more with Group S (399±26 minutes), (376±26 minutes) than Group H (270±35 minutes), (251±34 minutes), respectively. Present study's results of block duration with soda bicarbonate accord with the study results by Gupta S et al., i.e., 399.42±27 minutes [12]. While, for hyaluronidase block duration results coincide with the study by Mostafa TA et al., i.e., (190.23±37.62) and (147.9±27) minutes respectively as it also uses the same concentration 1500 IU of hyaluronidase drug with the same 30 mL total drug volume [11]. Contrasting prolonged block duration results were seen in other studies by Hakim KY et al., and Elmaghraby AA et al., due to different drug concentration and total volume [2,20].

Present study shows analgesia duration and time of first rescue analgesia was more with Group S (354±26 minutes) compared with Group H (223±41 minutes) which is relevant to the study results by Patel DD et al., with soda bicarbonate as (429±86.45 minutes)

[13]. For hyaluronidase results are almost similar to the study by Elmaghraby AA et al., [20] i.e., 5-8 hours, but are in contrast with the results in study by Hakim KY et al., [2].

VAS score of ≥4 postoperatively was seen in nine patients at five hours and in rest 11 patients by seven hours. This result is similar for soda bicarbonate with study by Patel DD et al., in which nine patients had VAS score ≥4 at six hours and other 11 patients at nine hours [13]. Complications observed during the study were minimal to none in both the groups.

Limitation(s)

The limitations of present study are: First, the lack of a placebo group. Second, this being a short research study undertaken for a shorter duration. Third, only normotensive patients were included and the results may not reflect the effectiveness and safety in hypertensives in whom intraoperative haemodynamics are crucial. Since this is a hospital-based study, its generalisability is limited.

CONCLUSION(S)

The present study concludes the clinical importance of utilising hyaluronidase as an adjuvant compared to soda bicarbonate in regional anaesthetic procedures for achieving faster onset of sensory and motor block, with minimal/no side-effects and earlier postoperative mobilisation for facilitating early assessment of limb movements following surgery to rule out any iatrogenic nerve injury by the surgeon. However, the duration of analgesia is more with soda bicarbonate compared to hyaluronidase.

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