To compare efficacy and safety of two different doses of Dexmedetomidine as an adjuvant to Ropivacaine compared to Ropivacaine in block and intravenously Dexmedetomidine in upper limb surgeries under supraclavicular brachial plexus block.

Dr Apurva Abhinandan Mittal[1] Dr Pushpendra Singh Chahar [2] Dr Apala Shanker Garg[3] Dr Rajani Yadav[4] Dr Mrinal Sharma[5] Dr Jaydev[6]

(Professor, Deptt of Anaesthesia, SNMC, Agra)
(Assistant Professor ,K D Medical College, Mathura
(Senior Resident, Deptt of Anaesthesia, SNMC, Agra)
(Senior Resident, Deptt of Anaesthesia ,SNMC ,Agra)
(Consultant, Arogya Plus Hospital and research Centre,Mathura)
(MD, Anaesthesia, SN Medical College, Agra)
Corresponding author:Dr Apala Shanker Garg
Email: Apalagarg1@gmail.com

ABSTRACT

To compare efficacy and safety of two different doses of Dexmedetomidine as an adjuvant to Ropivacaine compared to Ropivacaine in block and intravenously Dexmedetomidine in upper limb surgeries under supraclavicular brachial plexus block.

INTRODUCTION

Supraclavicular block is a reliable, rapid-onset approach to brachial plexus anaesthesia. The supraclavicular block provides anesthesia and analgesia to the upper extremity below the shoulder. It is an excellent choice for elbow and hand surgery.

Adjuvants are added to local anesthetics in peripheral nerve blocks to fasten the onset of action, to prolong the duration of action and improve the quality of blockade. Various adjuvants like morphine, fentanyl, sufentanil, clonidine, midazolam, ketamine, neostigmine, dexmedetomidine are added to local anesthetics. Since dexmedetomidine has α2:α1 selectivity ratio of 1620:1 as compared to 220:1 for clonidine, it decreases unwanted side effects of α1 and much more sedative and analgesic. ***Ropivacaine*** is a long-acting amide local

anaesthetic agent and first produced as a pure enantiomer structurally related to Bupivacaine.

Dexmedetomidineis d-enantiomer of medetomidine. It belongs to imidazole subclass of α2 receptor agonist. It is a newer α_2-adrenoreceptor agonist is currently in focus for its sedative, anxiolytic and analgesic properties.It is rapidly distributed and metabolized in liver, excreted in urine and faeces.

Keywords: Dexmedetomidine, Supraclavicular block , Ropivacaine

METERIAL AND METHOD

With the approval of hospital research ethical committee and informed consent this study is conducted in Department of Anaesthesia and Critical care of Sarojini Naidu Medical College, Agra

Study design: Randomized, Prospective, Double blind clinical study

Randomisation was done by computer generated random numbers

Research setting: Orthopaedics operation theatre and Orthopaedics post-op ward, SNMC, Agra.

Using a computer-generated randomization, patients were randomized into three groups of 30 patients each as:

Group A: {0.75%ropivacaine+1µg/kg dexmedetomidine}30cc+50ml NS

Group B: {0.75%ropivacaine+2µg/kg dexmedetomidine}30cc+50ml NS

Group C: {0.75%ropivacaine}30cc+2µg/kg dexmedetomidine in50mlNS

Group A:supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75% and 1µg/kgdexmedetomidine and 50 ml normal saline administered as IV infusion over 15 min.

Group B:supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75% containing 2µg/kgdexmedetomidine and 50 ml normal saline (0.9%) administered as IV infusion over 15 min.

Group C: supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75%and 50ml normal saline containing 2µg/kg dexmedetomidine administered as IV infusion over 15 min.

After aseptic preparation of the area, supraclavicular brachial plexus block was performed with 30 ml of study drug by an anesthesiologist who was unaware of the nature of study drug solution with patient in supine position and head turned to opposite side with the ipsilateral arm in adducted position. Part preparation is done using betadine solution and sterile draping was done and then supraclavicular brachial plexus block was done on the patient using blind perivascular paraesthesia technique.Intravenous infusion of 50 ml study drug was also started at the time of starting the block.

RESULTS

In this randomised and double-blind study, we had compared the effect of 1 µg/kg dexmedetomidine with 2 µg/kg dexmedetomidine in brachial plexus block as an adjuvant with 0.75%Ropivacaine in supraclavicular brachial plexus block with 2 µg/kg dexmedetomidine as intravenous administration

In our study we have found that addition of 2 µg/kg dexmedetomidine to 0.75% ropivacaine in supraclavicular brachial plexus block resulted in a faster onset of sensory block (table-3) which is supported by Esmaoglu *et al*.[15] It has been found that onset of sensory was significantly faster in groups receiving dexmedetomidine in block when compared to group that received dexmedetomidine intravenously suggesting the presence of α_2 -adrenoceptors in brachial plexus and hence a faster local action.

In our study we have found that by increasing the dose of dexmedetomidine as adjuvant though produced early onset of sensory block did not produce significant onset of motor block (table-4) in any of the three groups(as p value is>0.005)

CONCLUSION

Hence, we conclude that administration of [dexmedetomidine 2 μg/kg with 0.75%ropivacaine] in supraclavicular brachial plexus block is better modality in comparison to {dexmedetomidine1 μg/kg with 0.75% ropivacaine} in block and 0.75%ropivacaine in block plus intravenous dexmedetomidine without any side effects or hemodynamic changes in elective upper limb surgeries.

Introduction

Supraclavicular block is a reliable, rapid-onset approach to brachial plexus anaesthesia. The anatomy of the brachial plexus, with its three trunks confined to a much-reduced surface area, affords a high success rate for achieving anesthesia in the upper extremity below the shoulder.

The supraclavicular block provides anesthesia and analgesia to the upper extremity below the shoulder. It is an excellent choice for elbow and hand surgery.Adjuvants are added to local anesthetics in peripheral nerve blocks to fasten the onset of action, to prolong the duration of action and improve the quality of blockade. Various adjuvants like morphine, fentanyl, sufentanil, clonidine, midazolam, ketamine, neostigmine, dexmedetomidine are added to local anesthetics.

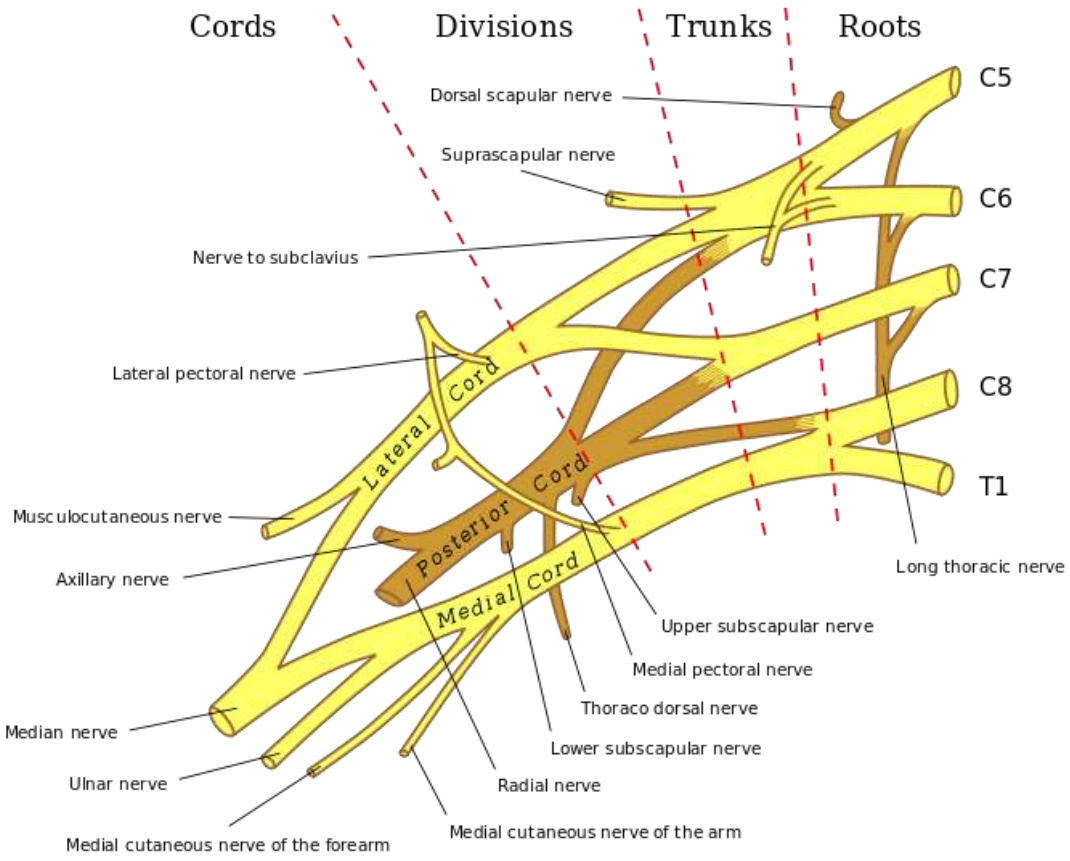
Anatomy

The Brachial plexus is a network (plexus) of nerves (formed by the anterior rami ofthe lower four cervical nerves and first thoracic nerve (C5, C6, C7, C8, and T1). This plexus extends from the spinal cord, through the cervicoaxillary canal in the neck, over the first rib, and into the armpit. It supplies afferent and efferent nerve fibres to the chest, shoulder, arm, forearm, and hand.

The brachial plexus is divided into five *roots*, three *trunks*, six *divisions* (three anterior and three posterior), three *cords*, and five *branches*.

Structure:

- Roots
- Trunks
- Divisions
- Cords
- Branches



Roots:

These are constituted by the anterior primary rami of spinal nerves C5, C6, C7, Cg and T1, with contributions from the anterior primary rami of C4 and T2. The origin of the plexus may shift by one segment either upward or downward, resulting in a prefixed or postfixed plexus respectively.

In a prefixed plexus, the contribution by C4 is large and that from T2 is often absent. In a postfixed plexus, the contribution by T1 is large, T2 is always present, C4 is absent, and C5 is reduced in size.

The roots join to form **trunks** as follows:

- “superior” or “upper” (C5-C6) trunk.
- “middle” (C7)trunk.

- “inferior” or “lower” (C8, T1)trunk.

Each trunk then splits in two, to form six **divisions**:

- anterior divisions of the upper, middle, and lower trunks
- posterior divisions of the upper, middle, and lower trunks

Cords:

i. The lateral cord is formed by the union of ventral divisions of the upper and middle trunks (two divisions).
ii. The medial cord is formed by the ventral division of the lower trunk (one division).
iii. The posterior cord is formed by union of the dorsal divisions of all the three trunks (three divisions).

Branches of roots:

1. Nerve to serratus anterior (long thoracic nerve) (C5, C6, C7)
2. Nerve to rhomboids (dorsal scapular nerve) (C5).
3. Branches to longus colli and scaleni muscles (both C5-C8) and branch to phrenic nerve (C4).

Branches of trunks

a. Nerve to subclavius (C5,6)
b. Suprascapular nerve (C5,6)

Branches of cords

- Lateral cord

  Lateral pectoral nerve (C5-7)

Musculo cutaneous nerve (C5-7)

Lateral head of median nerve (C6,7)

- Medial cord

Medial pectoral nerve (C8, T1)

Medial cutaneous nerve of arm (C8, T1)

Medial cutaneous nerve of forearm (C8, T1)

Medial head of median nerve (C8, T1)

Ulnar nerve (C7-8, T1)

- Posterior cord

Upper subscapular nerve (C5,6)

Nerve to lattismusdorsi (C6-8)

Lower subscapular nerve (C5,6)

Axillary nerve (C5,6)

Radial nerve (C5-8, T1)

LOCAL ANAESTHETIC& MODE OF ACTION

Ropivacaine is a long-acting amide local anaesthetic agent and first produced as a pure enantiomer structurally related to Bupivacaine. It produces effects similar to other local anaesthetics via reversible inhibition of sodium ion influx in nerve fibres. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres, resulting in a relatively reduced motor blockade. Thus, ropivacaine has more motor sensory differentiation. Because of less lipophilicity it has lesser potential for central nervous system toxicity and cardiotoxicity.

It is a pure S(-)enantiomer, is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.[1]

The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption $t_{1/2}$ of approximately 4.2 hours.

Ropivacaine is bound to plasma proteins to an extent of 94%, mainly to α1-acid glycoprotein. The total plasma concentration increase during continuous epidural infusion of ropivacaine[2][3] is caused by an increase in the degree of protein binding and subsequent decrease in clearance of ropivacaine.[3]It is metabolised extensively in the liver and excreted in urine.

Absorption and distribution

The plasma concentration of ropivacaine depends on the total dose administered and the route of administration, as well as the haemodynamic and circulatory condition of the patient and vascularity of the administration site. [2]

The incidence of cardiotoxicity and central nervous system (CNS) toxicity as a result of inadvertent intravascular injection of ropivacaine appears to be low.[4] On the basis of animal and volunteer studies, it can be concluded that ropivacaine seems to be less neurotoxic and cardiotoxic than bupivacaine.

Many additives to local anesthetics such as opioids, clonidine, neostigmine and tramadol etc. have been used to increase the duration of the block, to improve postoperative pain management[5]and to avoid the need for placing catheter for continuous local anesthetic drug infusion.

Dexmedetomidineis d-enantiomer of medetomidine. It belongs to imidazole subclass of α2 receptor agonist. It is a newer α_2-adrenoreceptor agonist is

currently in focus for its sedative, anxiolytic and analgesic properties.It is rapidly distributed and metabolized in liver, excreted in urine and faeces.

Dexmedetomidine has α2: α 1 selectivity of 1600:1, so it is 8 times more potent α2-adrenoceptor agonist than clonidine. Dexmedetomidine available as ampoule containing 1ml and 2ml solution with the strength of each ml containing 100mcg.

The analgesic mechanism of dexmedetomidine is due to stimulation of α2 receptors at the substantia gelatinosa of spinal cord, inhibition of release of substance P, and preventing nor adrenaline release at the nerve endings.

In human beings, dexmedetomidine has also shown to prolong the duration of block and postoperative analgesia when added to local anaesthetic in various regional blocks.[6][7][8]

Most human studies of dexmedetomidine as an adjuvant to local anaesthetics involved combinations with bupivacaine or levobupivacaine.[09][10] Due to unique pharmacologic properties and fewer side effects, ropivacaine is being preferred by an increasing number of anesthesiologists for peripheral nerve blocks

Aim and Objectives

. **AIM:**

To compare efficacy and safety of two different doses of Dexmedetomidine as an adjuvant to Ropivacaine compared to Ropivacaine in block and intravenously Dexmedetomidine in upper limb surgeries under supraclavicular brachial plexus block

Objectives: Comparison of 3 groups in terms of

- Time of onset of sensory and motor blockade.
- Duration of Sensory blockade.
- Duration of Motor blockade.
- Duration of Post-Operative Analgesia.
- Complications.

Material and Methods

With the approval of hospital research ethical committee and informed consent this study is conducted in Department of Anaesthesia and Critical care of Sarojini Naidu Medical College, Agra.

Study design: Randomized, Prospective, Double blind clinical study

Randomisation was done by computer generated random numbers

Research setting: Orthopaedics operation theatre and Orthopaedics post-op ward, SNMC, Agra.

INCLUSION CRITERIA:

1. ASA I&II
2. Both sexes
3. Age between 18-60yrs
4. Elective upper limb surgery
5. Under supraclavicular brachial plexus block
6. Without comorbidity illnesses

EXCLUSION CRITERIA:

1. Patient with peripheral neuropathy
2. Diabetes mellitus
3. Hepatic diseases
4. Bleeding disorders
5. Hypersensitive reactions
6. BMI-35 and above
7. Pregnancy or breast feeding
8. Infection at injection site

90 American Society of Anesthesiologist (ASA) grade I or II patients, scheduled for elective upper limb surgery below mid-humerus level under supraclavicular brachial plexus block were enrolled in this prospective, randomized, double-blind controlled trial.

Using a computer-generated randomization, patients were randomized into three groups of 30 patients each as:

Group A: {0.75%ropivacaine+1µg/kg dexmedetomidine}30cc+50ml NS

Group B: {0.75%ropivacaine+2µg/kg dexmedetomidine}30cc+50ml NS

Group C: {0.75%ropivacaine}30cc+2µg/kg dexmedetomidine in50mlNS

Preanesthetic assessment of all the patients was done the day before scheduled surgery. Patients were premedicated with tablet alprazolam 0.25 mg and tablet ranitidine 150 mg on night before surgery.

Patients with pre-existing peripheral neuropathy of upper limb, bleeding disorders, infection at injection site, pregnancy and known hypersensitivity to the study drugs, were excluded from the study.

Coded study drug solutions were prepared by an anesthesiologist not involved in further study and handed over to another anesthesiologist for administration.

Group A:supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75% and 1µg/kgdexmedetomidine and 50 ml normal saline administered as IV infusion over 15 min.

Group B:supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75% containing 2µg/kgdexmedetomidine and 50 ml normal saline (0.9%) administered as IV infusion over 15 min.

Group C: supraclavicular brachial plexus block given with 30 ml Ropivacaine 0.75%and 50ml normal saline containing 2µg/kg dexmedetomidine administered as IV infusion over 15 min.

Patients were preoperatively assessed and procedure was explained and consent was taken for performing supraclavicular brachial plexus block

After shifting the patient to operating table, standard anesthesia monitoring in the form of the baseline measurement of heart rate, non-invasive arterial blood pressure, and peripheral oxygen saturation (SpO_2) was started. Intravenous access was achieved using 20 G cannula in the nonoperative arm.

After aseptic preparation of the area, supraclavicular brachial plexus block was performed with 30 ml of study drug by an anesthesiologist who was unaware of the nature of study drug solution with patient in supine position and head turned to opposite side with the ipsilateral arm in adducted position. Part preparation is done using betadine solution and sterile draping was done and then supraclavicular brachial plexus block was done on the patient using blind perivascular paraesthesia technique.Intravenous infusion of 50 ml study drug was also started at the time of starting the block.

Evaluation of block:

- Vital signs monitoring -heart rate, non-invasive blood pressure, oxygen saturation and sedation score were measured every minute for the first 5 minute and every 5 minutes for 1 hour, every 15 minutes thereafter until the end of surgery& in the post-operative period. For statistical purposes they were documented at 0,5,10,15,30,45,60,90,120,150 minutes.

- Immediately following the administration of the drug, patient was evaluated for the onset of sensory and motor blockade every minute.

Onset of sensory block was assessed by pinprick test with a blunt 23 G hypodermic needle in the distribution of all four nerves (ulnar, median, radial and musculocutaneous nerves) using a 3-point scale as

♣ Score 0: normal sensation

♣ Score 1: loss of sensation to pin prick

♣ Score 2: loss of sensation to touch

Onset time for motor block- Time from completion of injection to complete motor blockade with inability to move fingers

Modified Bromage scale:

Score 0 – normal motor function with full flexion, extension of elbow, wrist and fingers.

Score 1 – decrease motor strength with ability to move fingers and/or wrist only.

Score 2 – complete motor blockade with inability to move fingers.

- Sedation was assessed by Modified Ramsay sedation scale.

  1 = anxious, agitated, restless

  2 =cooperative, oriented, tranquil

  3 = responds to commands only

  4 = brisk response to light glabellar tap or loud noise

  5 = sluggish response to light glabellar tap or loud noise

  6 =no response.

At the end of the operation, quality of anesthesia was graded by the anesthesiologist as:

Excellent (4): No complaint from the patient,

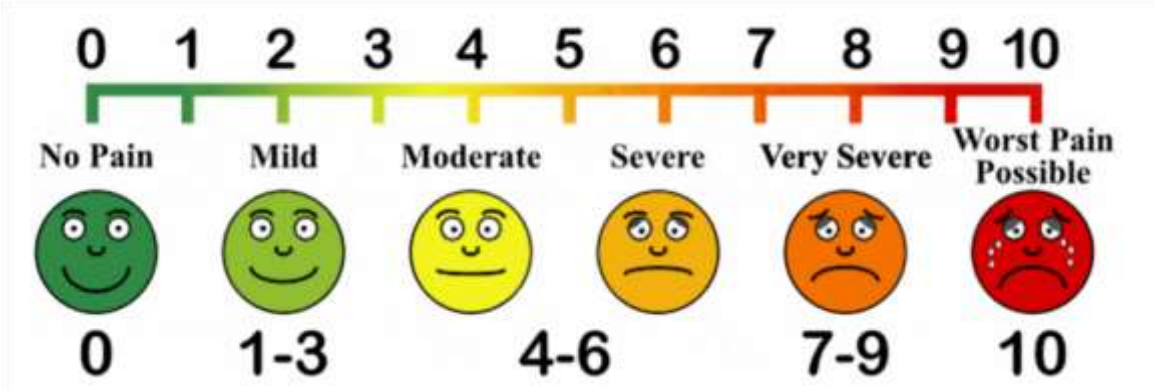
Good (3): Minor complaint with no need for supplemental analgesics,

Moderate (2): Complaint that required supplemental analgesics,

Unsuccessful (1): Patient required general anesthesia.

•Duration of Analgesia – time from onset of sensory block to vas score 4.

Visual Analog Scale Score



The observations in the recovery room were made by anesthesiologist who was unaware of the nature of drugs administered. On arrival in recovery room patients were asked to rate their pain on 11-point visual analogue scale (VAS) and thereafter pain was assessed regularly every 30 min for first 2 h and then every 1 hourly till 24 h. Testing for sensory and motor block regression was done every 15 min until complete resolution. Duration of sensory block was defined as the time interval between the end of block administration and complete resolution of sensation on all nerves using pin prick method. Duration of motor block was defined as the time interval between the end of block administration and the recovery of complete motor power of the hand and forearm using Modified Bromage score (score0).

Injection diclofenac sodium 75 mg intramuscular was administered when VAS score was ≥4. The time between the end of local anesthetic administration and first rescue analgesic administration was recorded as the duration of analgesia.

Patients were questioned for skin rash and observed for tachycardia (>20% above baseline value), bradycardia (<50 beats per minute), hypotension (>20% below baseline value), hypertension (>20% above baseline value), hypoxemia (SpO_2 <90%), sedation or any other side effect if any, during 24 h postoperative period.

Statistical analysis

Data were analysed usingOpen Source Epidemiologic Statistics for Public Health,2013 software. Age, sex, weight, sensory and motor block onset time, duration of sensory and motor block and duration of post-operative analgesia, quality of anesthesia were compared using the ANOVA test. ANOVA test was used to test the difference between variables.

The alpha level used for this analysis was $P < 0.05$. The *post-hoc* analyses revealed the statistical power for this study was 0.40 for detecting a small effect, whereas the power exceeded 0.99 for the detection of a moderate to large effect size. Thus, there was more than adequate power (i.e., power ×0.80) at a moderate to large effect size level, but less than adequate statistical power at the small effect size level. A sample size of 90 was used.

Observation and Results

Table 1: Time of onset of sensory block in minutes

Time of sensory onset in mins	Group-A	Group-B	Group-C
Mean	4.895	4.563	5.38
SD	1.112	1.289	0.574
p-value	0.00016		

Table 1 shows the comparison of onset of sensory blockade between three groups. Mean onset of sensory block was significantly longer in group-IV than group-A which is significantly longer than group-B.

B(4.563±1.289)< A(4.895±1.112)<C(5.38±0.574) with p<0.05

Table 2: Time of onset of motor block in minutes

Time of onset of motor block in	Group-A	Group-B	Group-C

mins			
Mean	12.10	8.45	13.05
SD	1.67	1.37	1.73
p-value	0.4234		

Table 2 shows the comparison of onset of motor blockade between three groups. Mean onset of motor block was insignificant in between groups as p-value was >0.05.

And also there is no significant relation in between (Group-A & Group-B with p-value=0.29) & (Group-A & Group-C with p-value=0.85)& (Group-B & Group-C with p-value=0.21)

Table 3: Duration of sensory block in hours

Duration of sensory in hrs	Group-A	Group-B	Group-C
Mean	12.10	12.56	10.61
SD	0.77	1.36	0.40
p-value	<0.00005		

Table 3 shows the comparison of onset of sensory blockade between three groups. Mean duration of sensory block was significantly longer in group-B than group-A which is significantly longer than group-C.

B(12.56±1.36)> A(12.10±0.77)>C(10.61±0.40) with p<0.00005

Table 4: Duration of motor block in hours

Duration of motor block in hrs	Group-A	Group-B	Group-C
Mean	9.16	10.28	7.57
SD	0.73	1.45	0.88
p-value	0.00054		

Table 4 shows the comparison of onset of motor blockade between three groups. Mean duration of motor block was significantly longer in group-B than group-A which is significantly longer than group-c.

B(10.28±1.45)> A(9.16±0.73)> IV(7.57±0.88) with p=0.00054

Table 5: Duration of post-operative analgesia in hours

Duration of post-op Analgesia in hrs	Group-A	Group-B	Group-C
Mean	10.28	11.78	10.45
SD	0.54	1.70	1.23
p-value	<0.00001		

Table 5 shows the comparison of duration of post-operative analgesia between three groups. Mean duration was significantly longer in group-B than group-C which is longer than group-A.

B(11.78±0.54)>C(10.45±1.23)>A(10.28±0.54) with p=<0.00001

Table 6: Duration of post-operative sedation score

Duration of post-op sedation score	Group-A	Group-B	Group-C
Mean	2.32	3.70	4.90
SD	0.47	0.87	0.99
p-value	0.0005		

Table 6 shows the comparison of post-operative sedation score between three groups. Mean duration of post-operative sedation score between these three groups was significant.

A(2.32±0.47)<B(3.70±0.87)<C(4.90±0.99) with p=0.0005

Discussion

In this randomised and double-blind study, we had compared the effect of 1 µg/kg dexmedetomidine with 2 µg/kg dexmedetomidine in brachial plexus block as an adjuvant with 0.75%Ropivacaine in supraclavicular brachial plexus block with 2 µg/kg dexmedetomidine as intravenous administration.

In our study we have found that addition of 2 µg/kg dexmedetomidine to 0.75% ropivacaine in supraclavicular brachial plexus block resulted in a faster onset of sensory block (table-1) which is supported by Esmaoglu *et al.*[10] It has been found that onset of sensory was significantly faster in groups receiving dexmedetomidine in block when compared to group that received dexmedetomidine intravenously suggesting the presence of α_2 -adrenoceptors in brachial plexus and hence a faster local action.

In our study we have found that by increasing the dose of dexmedetomidine as adjuvant though produced early onset of sensory block did not produce significant onset of motor block (table-2) in any of the three groups(as p value is>0.005)

In our study we have found that addition of 2 μg/kg dexmedetomidine to 0.75% ropivacaine has produced prolonged duration of sensory block and motor block respectively (table-5 & table-6) which was also supported by earlier studies by Ammar and Mahmoud[25] Esmaoglu et al. [10] Rancourt et al.[11] Marhofer et al.[5]

In the accordance with study by Swami *et al*.[12] and Esmaoglu *et al*.[10]in our study no significant serious side effects were reported in any group.

Along with studying the effect of dexmedetomidine as an adjuvant added along with ropivacaine in peripheral block we have also studied the effect of dexmedetomidine given as intravenous dose and found that it resulted in delayed post-operative analgesia requirement.

However, in table-5 duration of post-operative analgesia was longest in Group-B(11.78±1.70) followed by Group-C(10.45±1.23)which was supported by study byMarhofer *et al*.[7] that a profound prolongation of ulnar nerve block (UNB) of 60% with perineural dexmedetomidine when added to 0.75% ropivacaine. Whereas, systemic administration of 20 μg dexmedetomidine resulted in a prolongation of only 10% during UNB with 0.75% ropivacaine. It has also been found in our study that due to lesser dose of dexmedetomidine in Group-A the post-operative analgesia is lesser in Group-A as compared to group receiving intravenous dexmedetomidine.

We observed that in our study post-operative sedation score was significantly higher in Group-C when compared to other groups with the mean value of 4.90 (table-8) which can be explained on the basis that dexmedetomidine is

given systemically in higher dose leading to the higher post-operative sedation score.

Hence, we conclude that administration of [dexmedetomidine 2 μg/kg with 0.75%ropivacaine] in supraclavicular brachial plexus block is better modality in comparison to {dexmedetomidine1 μg/kg with 0.75% ropivacaine} in block and 0.75%ropivacaine in block plus intravenous dexmedetomidine without any side effects or hemodynamic changes in elective upper limb surgeries.

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