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Research Article

Block Facilitatory Effects of Perineural Dexmedetomidine in Supraclavicular Brachial Plexus Block with Ropivacaine: Does Dexmedetomidine Has Perineural Site of Action? A Randomized, Controlled and Triple Blind Study

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ABSTRACT

Background: Although nerve block facilitatory effects of dexmedetomidine when used as a perineural adjunct to local anesthetics in supraclavicular brachial plexus blocks are well recognized in multiple studies, but whether this action is at directly on peripheral nerve fibers or is at central level after systemic absorption is unclear. Aim of this study was to evaluate the effect of adding dexmedetomidine 1 microgram/kg to ropivacaine 0.5% in supraclavicular brachial plexus block in terms of duration of analgesia and 24hour cumulative analgesic requirement and to test the hypothesis whether the effect of dexmedetomidine, is due to direct local action on nerve plexus or is centrally mediated after systemic absorption.

Methods: 105 patients of ASA grade I and II of either sex undergoing upper limb orthopedic surgeries were divided in 3 groups of 35 patients in each group. Group Rc (control group) received supraclavicular block with 30ml of 0.5% ropivacaine and intravenous infusion of 30ml of normal saline; group RDexP received supraclavicular block with 30ml solution of 0.5% ropivacaine+ dexmedetomidine 1mcg/kg and intravenous infusion of 30ml of normal saline; and group RDexIV received supraclavicular block with 30ml of 0.5% ropivacaine and intravenous infusion of 30ml of normal saline solution containing dexmedetomidine 1mcg/kg. Primary outcome was duration of analgesia and 24hour cumulative analgesic requirement.

Results: The demographic data were comparable in all three groups. Duration of analgesia was longest in group RDexP followed by group RDexIV and least in control group. 24hour cumulative analgesic requirement was least in group RDexP and maximum in group R. 2 patients, one from each group RDexP and group RDexIV reported bradycardia and 6 patients from group RDexIV reported hypotension.

Conclusion: We conclude that action of dexmedetomidine is most probably peripheral on brachial plexus nerve fibers directly rather than centrally mediated after systemic absorption.

The authors declare no conflicts of interest.

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Introduction

Upper extremity neve blockade has become a commonly employed regional anesthetic techniques for upper limb surgeries since first performed in 1884 by W. J. Halstead who used direct exposure of plexus in the neck to accomplish the block [1]. Supraclavicular brachial plexus block (SCBP block) is performed at the trunk level where the plexus is compact and therefore provides most complete and reliable anesthesia and thereby also called as "spinal anesthesia" of the upper extremity. Ultra-sonography (USG) for supraclavicular brachial plexus block with real time localization of structures, drug spread and assessment of proper needle-tip position has improved the success rate and improved safety margin by decreasing the risk of pneumothorax [2] and thus became gold standard.

Dexmedetomidine is an alpha 2 agonist that have been used along with local anesthetics in perineural blocks to enhance their analgesic efficacy and to facilitate early achievement and prolongation of block [3-6]. There are multiple clinical trials and meta-analyses evidence supporting the facilitatory effects of perineural dexmedetomidine as peripheral nerve block adjunct in terms of prolonged sensory and motor block durations, and faster sensory and motor block onset and analgesic benefits [7-11].

Although the facilitatory effects of perineural dexmedetomidine are well recognized, but whether this is mediated by local action at peripheral level or by central mechanism after systemic absorption remains unknown. While designing this study we aimed to assess the effect of adding perineural or intravenous dexmedetomidine 1 microgram/kg as an adjuvant to ropivacaine 0.5% in supraclavicular brachial plexus block on the block characteristics like onset and duration of sensory and motor blockade, time to first analgesic demand, 24 hour cumulative postoperative analgesic requirement; and to test the hypothesis that the effect of dexmedetomidine, is due to direct local action on nerve fibres at plexus level rather than at central level after systemic absorption from block site.

Methods

The study was approved by institutional ethics committee and review board (reference no. SNMC/IEC/2019/Plan/124 dated 30/05/2019) and CTRI registration (CTRI/2020/10/028270) was done on 7/10/20 by primary investigator. We conducted a prospective, triple blind, randomized interventional trial on 105 patients undergoing elective upper limb orthopedic surgery under USG guided supra-clavicular brachial plexus block. This study was carried on at a single tertiary care hospital in western India from October 2020 to May 2021. This trial report was conducted in accordance with the Consolidated Standards of Reporting Clinical Trials (CONSORT) guidelines (Figure 1).

After detailed explanation about the study protocol and anesthetic technique the written informed consent was taken from all the patients for participation in study. Inclusion criteria were ASA I and II class patients of age group 18 to 60 years of either sex undergoing orthopedic upper limb surgery of less than 2 hours duration with BMI below 30 and free from any associated acute or chronic systemic illness. Patients having hypersensitivity or contraindication to ropivacaine and dexmedetomidine; local pathology at the site of injection or disability limiting the performance of block; pregnant, lactating mothers, diabetic patient, neurological deficit in operative limb and patients with chronic pain or on long-term analgesics were excluded from the study.

Sample Size

A pilot study was done to determine the sample size. As our primary outcome was duration of analgesia, we assumed a 30% difference in the duration of analgesia as significant which came out as 1.1 hour. To get the power of study of 80% at 95% confidence interval with α error of 0.05 and β error of 0.2, minimum of 33 patients were required in each of the three groups. We also included control group patients in our study, so we took another 33 patients in control group. We included 35 patients in each group to compensate for possible attrition hence total 105 patients were included in all three groups.

Randomization and blinding

By using computer software to generate random numbers, recruited patients were randomly allocated to three groups of 35 each. Allocation was concealed by using serially numbered opaque envelops that were only opened after arrival of patient in preoperative area. Study medication was prepared in two sets of 30 ml quantity and labelled as study drug 1 and drug 2 as mentioned below (Table 1) by one anesthesiologist and handed over to primary anesthesiologist for administration. Study drug 1 was used for perineural injection and study drug 2 intravenous infusion was started just after completion of block at the rate of 30ml/hour.

All observers and study participants were blinded to study group allocation. Data were collected by the investigator, who was unaware of administered study drug.

Table 1- Study drug preparation

	Group Rc	Group RDexP	Group RDexIV
Study drug 1 in three 10 ml syringes (for perineural block)	20 ml of 0.75% ropivacaine + 10 ml of normal saline	20 ml of 0.75% ropivacaine + 10 ml of normal saline containing 1µg/kg dexmedetomidine	20 ml of 0.75% ropivacaine + 10 ml of normal saline
Study drug 2 in 50ml syringe (for intravenous infusion)	30 ml of normal saline	30 ml of normal saline	30 ml of normal saline containing 1µg/kg dexmedetomidine

Supraclavicular brachial plexus nerve blockade protocol

All recruited patients were assessed on the day before surgery and preanesthetic check-up was done, their demographic data and baseline vitals were noted. Nil by mouth was observed for 6 hours for solids and 2 hours for clear liquids as per hospital protocol. In the operative room, patients were not given any premedication, standard ASA monitoring with multi-para monitor (dragger/schiller) were applied and hemodynamic parameters, and room air oxygen saturation were noted. Intra venous access using 18G/20G cannula was obtained in the contra lateral upper limb and lactated ringer solution was started.

A supraclavicular brachial plexus nerve block was performed under aseptic precautions using 5–12 MHz linear array ultrasound probe with the patient in the supine position, with the patient's head turned away from the side to be blocked. Brachial plexus was approached with the needle of 18G intracath using the inplane technique. Once the needle reached the brachial plexus cluster, pre decided study drug 1 as mentioned above (Table 1) was injected in 3ml aliquots after careful negative aspiration. Visualization of study medication spread was observed in real time. To ensure that the drug spreads in all parts of the plexus, needle was repositioned if required.

After completion of block, study drug 2 was started as infusion at the rate of 30ml/hr.

HR, BP, SpO2 were recorded intra operatively followed by HR, BP, and NRS scores were recorded at 2,4,6,12 and 24 hours post operatively. Post operatively patients were given tramadol 100 mg intravenous as rescue analgesia, if NRS ≥4 or patient requested analgesia. Time to first rescue analgesia as well as the total doses of tramadol used in first 24 hours was recorded. Any side effects like horner's syndrome, vomiting, hoarseness of voice, nausea, pneumothorax, bradycardia, and hypotension were observed for and treated accordingly.

2.4 Outcome assessment

Primary Outcome of our study was duration of analgesia which was defined as the time interval from completion of local anesthetic administration till first need of rescue analgesic.

Secondary Outcomes were: (1) onset and duration of sensory and motor blockade, (2) 24-hour cumulative tramadol consumption, (3) pain severity on NRS scale, (4) patient satisfaction score, (5) hemodynamic measurements (systolic and diastolic blood pressure, heart rate), and (6) level of sedation.

Evaluation of sensory and motor block was done as described by Kathuria S et al [3] at every 3 min after administering drug 1 in plexus until complete sensory and motor block. Sensory block was assessed by pinprick test with a toothprick in the distribution of dermatomes C5 to T1 using a 3-point scale as: 0 = Normal sensation, 1= Loss of sensation of prick (analgesia), 2= Loss of sensation of touch (anesthesia) [3]. Motor block was evaluated on a 3-point scale as: 0 = Normal motor function, 1 = Reduced motor strength (but able to move fingers), 2 = Complete motor block. Onset time for sensory block was defined as the time interval between the end of total local anesthetic administration and anesthetic block (score 2) on all nerve territories. Onset time for motor block was defined as the time interval between the end of total local anesthetic administration and achievement of score 2 motor block [3]. The severity of pain for 24 h postoperatively was reported using a 10-point scale, ranging from 0 for no pain to 10 for the severe pain.

Patients were taught and instructed to assess the sensory and motor functions of their blocked arm, compared with the contralateral arm, every 30 min postoperatively. The durations of sensory and motor blockade were defined as the times from the end of injection until the patient detected complete resolution of the sensory and motor blockades (end of self-assessment), respectively.

Intraoperative sedation level was evaluated using the modified Ramsay Sedation Scale [12] 5 and 10 min after the start of sedation and every 10 min throughout the surgery and for 2hour postoperatively in post anesthesia care unit.

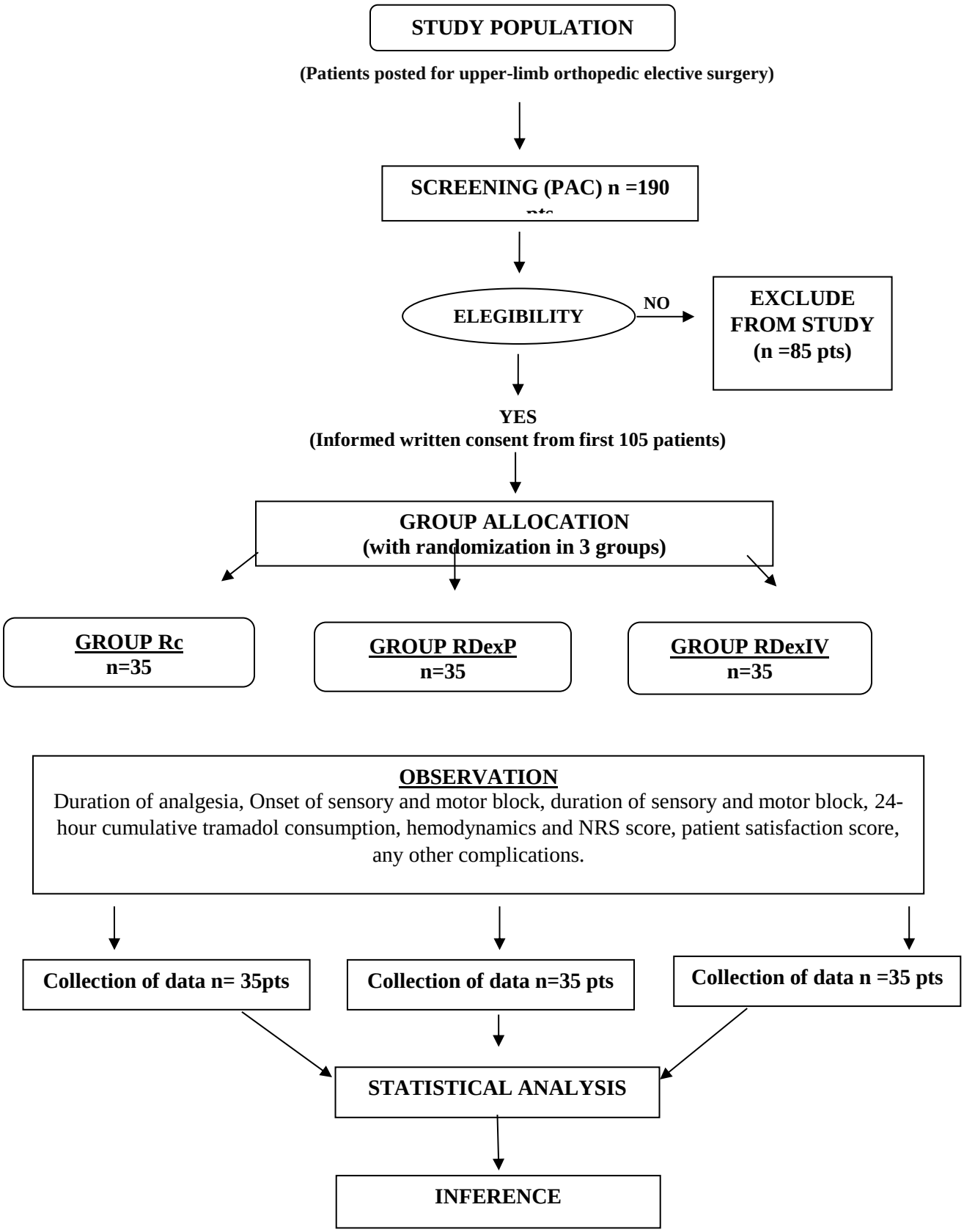

Figure 1- Consolidated Standards of Reporting Clinical Trials (CONSORT) diagram

Statistical Analysis

Statistical Package for the Social Sciences for 22.0 window version was used for analysis of data. Standard descriptive statistics like mean and standard deviation were used to compare baseline characteristics. The duration of analgesia was analysed by unpaired student t-test. Numerical variables were presented as frequency, percentage and mean± standard deviation. Categorical data was presented as percent of total. The results were considered significant if p value is <0.05 and highly significant if p value is < 0.001.

Results

All participants achieved adequate analgesia after administration of block and none was excluded from analysis. The three groups were well matched in terms of age, weight, height, gender and ASA grading (Table 2).

Table 2- Demographic characteristics of study participants

Characteristic	Group Rc	Group RDexP	Group RDexIV	P value Rc/RDexP	Rc/RDexIV	RDexP/RDexIV
Age in years mean±SD (median)	35.28±11.48 (35)	35.2±13.31 (30)	34.74±13.39 (32)	0.977	0.856	0.886
Male: Female	32:3	30:5	31:4	0.709	1.00	0.100
Height in cm mean±SD	168.14±6.93	169.25±5.08	169.45±6.28	0.446	0.490	0.884
Weight in kg mean±SD	66.45±7.05	66.48±6.18	65.65±6.35	0.985	0.619	0.582
BMI (kg/m^2) mean±SD	23.48±1.76	23.18±1.58	22.85±1.72	0.455	0.136	0.410
ASA grade I:II	21:14	17:18	20:15	0.337	0.808	0.472

Block characteristics are summarized in (Table 3). Duration of analgesia was significantly prolonged in group RDexP (807.77±107.58 min) and group RDexIV (752.42±113.60 min) than control group (510.74±59.17 min). Duration of analgesia was significantly more in group RDexP when compared with group RDexIV.

The sensory and motor block onset was significantly earlier in group RDexP than in group RDexIV and group R. sensory block onset time was 8.00±1.65 min in group RDexP as compared to 17.00±3.25 min and 12.11±1.99 min in group R and RDexIV, respectively.

Duration of sensory and motor block was highest in group RDexP followed by group RDexIV and least in control group. The total analgesic consumption in 24hour postoperatively was significantly more in group R than group RDexP and RDexIV. The difference in total analgesic consumption between group RDexP and RDexIV was not statistically significant.

Table 3- Block characteristics

Block characteristic (min)	Group Rc mean±SD (median)	Group RDexP mean±SD (median)	Group RDexIV mean±SD (median)	P value Rc/RDexP	Rc/RDexIV	RDexP/RDexIV
Duration of analgesia	510.74±59.17 (514)	807.77±107.58 (813)	752.42±113.60 (776)	<0.0001	<0.0001	0.0041
Onset of sensory block	17.00±3.25 (16)	8.00±1.65 (8)	12.11±1.99 (12)	<0.0001	<0.0001	<0.0001
Onset of motor block	27.17±4.65 (27)	15.02±2.44 (14)	20.31±4.30 (20)	<0.0001	<0.0001	<0.0001
Duration of sensory block	430.71±79.89 (420)	790.51±145.24 (816)	638.85±76.05 (630)	<0.0001	<0.0001	<0.0001
Duration of motor block	380±34.89 (390)	747.2±85.52 (720)	603.77±77.10 (626)	<0.0001	<0.0001	<0.0001
24hour cumulative tramadol dose (mg)	268.57±47.10 (300)	102.85±61.76 (100)	131.42±47.10 (100)	<0.0001	<0.0001	0.033

There was decrease in heart rate in patients receiving dexemedetomidine with maximum fall in group RDexIV (Figure 2). Bradycardia was noted in 2 patients, one patient each from perineural group (group RDexP) and intravenous group (group RDexIV). 0.6 mg intravenous injection of atropine sulphate was used to manage bradycardia.

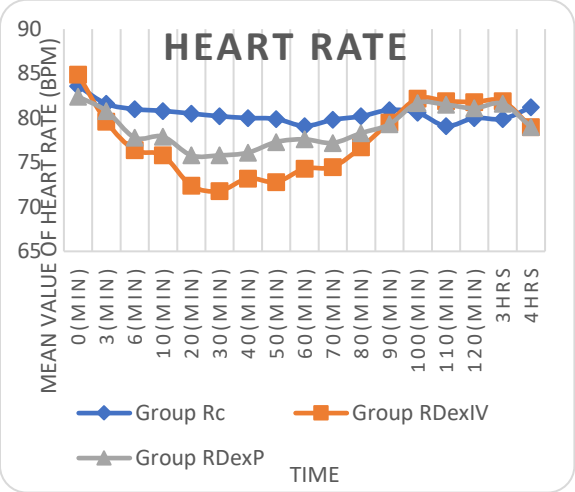

Figure 2- Comparison of heart rate in study groups intraoperatively

Change in mean blood pressure was statistically significantly ($p<0.05$) with unpaired-t test analysis at 90 min to 120 min in group RDexP and group RDexIV when compared with control group showing significant fall in MBP in dexmedetomidine receiving groups (Figure 3). Overall 6 patients (all from group RDexIV) developed hypotension which was promptly managed by 6 mg IV bolus of injection mephentermine. No episode of hypotension was observed in group RDexP or in control group.

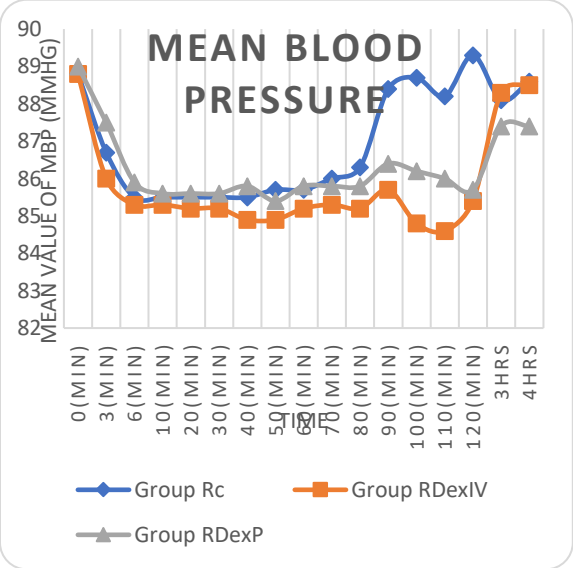

Figure 3- Comparison of mean blood pressure in study groups intraoperatively

At 40 and 50 minutes, sedation score was significantly higher in group receiving intravenous dexmedetomidine than perineural dexmedetomidine group. At one hour this difference became insignificant. Other than at 40 and 50 minutes, sedation score was similar in all three groups. No patient in any group had sedation score more than 3 (Figure 4).

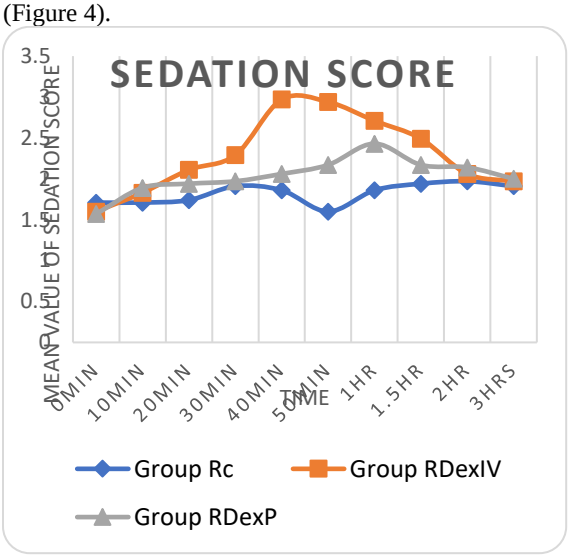

Figure 4- comparison of sedation score in study groups

Discussion

In literature there is enough evidence to suggest the efficacy of perineural dexmedetomidine as peripheral nerve block adjunct [3-11]. Similarly, our study demonstrates that perineural dexmedetomidine (1µg/kg) as a supraclavicular brachial plexus block adjunct is associated with longer duration of analgesia, reduced cumulative 24-hour postoperative analgesic consumption, prolonged sensory and motor block durations, and faster onset of sensory and motor blockade.

We studied the effect of adding dexmedetomidine (1µg/kg) both by perineural or intravenous routes to the 0.5% ropivacaine in ultrasound guided SCBPB. It was found that intravenous dexmedetomidine also resulted in longer duration of analgesia as assessed by delayed first request for analgesia supplementation, significantly decreased 24-hour analgesic consumption, faster onset of sensory and motor block and prolonged duration of both sensory and motor block when compared with control group (ropivacaine 0.5% alone in block). However, we found that duration of analgesia; and sensory and motor blockade durations were significantly higher when dexmedetomidine was administered perineurally rather than intravenously. Similarly, onset of sensory and motor blockade was faster in perineural group. These findings support the presence of α2 -adrenergic receptors (α2-

ARs) in brachial plexus and hence a faster local action in case of perineural dexmedetomidine.

The mechanism of action of perineural dexmedetomidine on the quality of local anesthetic induced nerve block is not fully clear. Although central α2-mediated analgesic effects of dexmedetomidine are well established, in 2011 an animal trial by Brummet et al [13] to assess the level of effector site of perineural dexmedetomidine found that dexmedetomidine induced prolongation of analgesic duration was reversed by pretreatment with current enhancer and was unaffected by pretreatment with α2-Ars blockers thus establishing that the anti-nociceptive effects of perineural dexmedetomidine are caused by the peripheral blockade of hyperpolarization-activated cation current and not by its action at central or peripheral α1 - or α2 receptors [13]. Our study supports this theory that the effect of perineural dexmedetomidine is primarily peripheral and not central after systemic absorption.

Andersen JH et al [14] conducted a paired, blinded trial in healthy volunteers who all received bilateral saphenous nerve blocks with 20ml ropivacaine 0.5% plus dexmedetomidine 100 µg, in one thigh and 20ml ropivacaine 0.5% alone in the other thigh. Their study design provided control of the systemic contribution of dexmedetomidine in the prolongation of a nerve block by ensuring that the systemic effects of dexmedetomidine were equal for both sided saphenous nerve blocks. The mean duration of block in the leg receiving ropivacaine plus dexmedetomidine was 22hour (95% CI, 21 to 24) compared to 20hour (95% CI, 19 to 21) in the leg receiving ropivacaine plus placebo with a mean difference of 2h (95% CI, 1 to 3; P = 0.001). In their trial, they demonstrated that perineural coadministration of dexmedetomidine and ropivacaine leads to a significant prolongation of a saphenous nerve block of 2h, attributable to only a peripheral mechanism while simultaneously controlling for systemic effects.

A few recent systemic reviews by Feng Y et al [7] and Hussain N et al [8] generated the evidence that perineural dexmedetomidine is a better peripheral nerve block adjunct along with superior safety profile with lower incidence of oversedation, hypotension and bradycardia when compared with intravenous dexmedetomidine.

Similar to our study, Abdallah FW et al [15] conducted a study where patients received interscalene brachial plexus block with 15ml of ropivacaine 0.5%. They used dexmedetomidine 0.5mcg/kg for both as perineural and intravenous groups. But in contrast to our study, they found that intravenous and perineural dexmedetomidine similarly prolong the duration of analgesia. This difference in the findings may be explained by higher dose of perineural as well as intravenous dexmedetomidine used in our study.

The mechanism of the analgesic actions of α2 agonists is probably multifactorial. α2 adrenergic receptors are G-protein gated potassium channels responsible for membrane hyperpolarization and attenuation of excitable cells firing; are found ubiquitously at cerebral, spinal and peripheral levels [16]. By acting at these multiple sites, dexmedetomidine causes inhibition of nociceptive neuronal conduction and leading to analgesia. Another mechanism for analgesic effects of dexmedetomidine involves hyperpolarisation activated cation currents which are responsible for repolarisation and normal activity of neurons during an action potential[13]. By direct blocking of these voltage gated calcium channels by α2 agonists action potential conduction is broken and neurotransmitter release inhibited. Thus, by preventing the firing of nociceptive excitable cells along with inhibition of conduction of nociceptive signals to the neighbours, dexmedetomidine produces analgesia.

Hence, we propose that the block facilitatory effects of dexmedetomidine are primarily by its direct peripheral action on brachial plexus nerves instead of its central effects at α2 receptors after systemic absorption from block site.

In our study, when compared with control group, patients receiving intravenous dexmedetomidine infusion reported significant earlier onset and prolonged duration of sensory and motor blockade, therefore establishing some role of central effects of dexmedetomidine. However, to determine the exact mechanism of dexmedetomidine for peripheral nerve block facilitatory effects with local anesthetics, further detailed studies are required.

In our study total of 2 patients, one from each group receiving perineural and intravenous dexmedetomidine reported bradycardia which was managed with injection atropine 0.6mg intravenously. Six patients from group D-IV reported hypotension which was treated with a single intravenous injection of mephentermine 6mg. Mean blood pressure and heart rate were lower in group D-IV and group D-P than control group.

Esmaoglu et al. reported bradycardia in 7 out of 30 patients who received perineural dexmedetomidine [4], lower incidence of bradycardia in our study can be explained by lower doses of dexmedetomidine used. These hemodynamic changes can be attributed to reduced central sympathetic outflow. Low incidence of hypotension and bradycardia in dexmedetomidine receiving groups may be explained by omission of loading dose of dexmedetomidine as most of the adverse effects associated with dexmedetomidine occur during or shortly after loading infusion [17-18]. Higher sedation score in dexmedetomidine receiving groups is a welcome side effect in regional blocks as it provides a calmer and more cooperative patient without oversedation.

In our study no respiratory depression was found in either group and patients were cooperative and easily arousable. Similar findings were reported by Hall JE et

al. after intravenous dexmedetomidine administration [19].

As peripheral nerve block facilitatory effects predominate in group receiving perineural dexmedetomidine (group D-P) and hemodynamic alterations and sedation are mainly prominent in intravenous dexmedetomidine receiving group (group D-IV), we theorize that it is mainly the direct peripheral action of dexmedetomidine on nerve fibres which is responsible for block facilitating effects rather than its action at central level after systemic absorption from perineural site. Hemodynamic alterations and sedation are mediated at supraspinal level and are prominent in group D-IV.

However, the central effects of dexmedetomidine also play some role in prolongation of duration of analgesia, prolongation of sensory and motor blockade and faster onset of sensory and motor blockade as 1 mcg/kg of dexmedetomidine intravenous infusion significantly affects all these parameters when compared to control group. However, additional studies with bigger sample size are warranted to investigate the mechanisms of peripheral action of dexmedetomidine, as well as dose response of peripheral dexmedetomidine on block facilitation.

The major limitation of this study was that we did not measure the plasma levels of dexmedetomidine that could have further supported the hypothesis that dexmedetomidine has a peripheral action rather than centrally mediated. Second, patients were followed up only for the first 24 h postoperatively and overall outcome such as total number of hospital days and long term neurological adverse effects were not noted.

Conclusion

Thus, we conclude that addition of dexmedetomidine 1mcg/kg as adjuvant to 0.5% ropivacaine in supraclavicular brachial plexus block prolongs duration of analgesia, decreases 24hour cumulative analgesic consumption, has faster onset and delayed wearing off sensory and motor blockade without any major side-effects. The action of dexmedetomidine is most probably peripheral on brachial plexus nerve fibers directly rather than centrally mediated after systemic absorption. The benefits of dexmedetomidine should be carefully weighed against prolonged motor block duration and the increased risks of hemodynamic instability and sedation.

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