

Comparison of Magnesium Sulfate and Dexmedetomidine as an Adjuvant to 0.5% Ropivacaine in Supraclavicular Brachial Plexus Block

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Abstract

Background & Objectives: Supraclavicular brachial plexus block is a popular technique for providing anesthesia for upper extremity surgeries. Perineural administration of dexmedetomidine and magnesium sulphate are known to enhance the effect of local anesthetics. The purpose of this study was to compare the impact of perineural dexmedetomidine and magnesium sulfate on the onset and duration of supraclavicular brachial plexus block using ropivacaine.

Methods: After IEC approval, a prospective, randomized, double blinded study was conducted on 60 ASA I and II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block. Patients were randomly divided into two groups. The first group [Gr M] was administered magnesium sulfate 150 mg and the second group [Gr D] was administered dexmedetomidine 100µg along with 0.5 % Twenty five ml of ropivacaine. The onset time and duration of sensory and motor blockade were recorded. Hemodynamic variables were recorded intraoperatively.

Results: The onset of sensory and motor block was significantly faster in Gr D compared to Gr M ($p < 0.05$). The duration of sensory and motor block was significantly more in Gr D compared to Gr M. Mean arterial pressures were comparable between the groups in the intraoperative period. However, mean heart rate was significantly less in the dexmedetomidine group. No other adverse event was observed.

Conclusion: Intravenous dexmedetomidine in combination with 25 ml ropivacaine (0.5%) hastened onset of sensory and motor block, and prolonged the duration of sensory and motor block when used for brachial plexus block, without producing any adverse events.

Keywords: Brachial plexus block; Ropivacaine; Dexmedetomidine; Magnesium sulfate

Date of Submission: 07-02-2020

Date of Acceptance: 22-02-2020

I. Introduction

Supraclavicular brachial plexus block using bupivacaine is a popular anesthetic technique for upper extremity surgeries and relief of perioperative pain. It also contributes to reduced hospital stay and less financial implications while avoiding the side effects of general anesthesia [1]. Generally, a single shot technique is employed and the duration of sensory and motor block mainly depends on the local anaesthetic used. Prolonging the duration of sensory blockade of ropivacaine is desirable for improved postoperative pain management and in order to avoid administration of opioids or non steroidal anti inflammatory agents in the postoperative period. In order to increase the duration of postoperative analgesia following supraclavicular brachial plexus block, many additives to local anesthetics have been tried e.g. opioids, dexamethasone and alpha agonists. Use of these additives has led to prolonged postoperative pain relief while avoiding the need for placing catheter for continuous infusion of local anesthetic agents.

The α_2 adrenoreceptor agonist agent clonidine, which has in-vitro local anesthetic properties, has been added to local anesthetic solution to prolong their action. However, clonidine has been found less useful at prolonging the duration of action of bupivacaine [2]. Dexmedetomidine, a newer agent in this group, possess

sedative, anxiolytic and analgesic properties. Dexmedetomidine has been found to be useful at prolonging the duration of action of bupivacaine. In animal studies, perineural administration of dexmedetomidine has been found to prolong the duration of block and postoperative analgesia when added to bupivacaine for regional procedures [3].

Perineural administration of dexmedetomidine along with levo bupivacaine for axillary brachial plexus block has shown to prolong the duration of postoperative analgesia [4,5].

Magnesium is a physiological calcium channel blocker and has also N-methyl-D-aspartate (NMDA) receptor antagonist effect.[6] Since magnesium sulfate can prevent central sensitization by the peripheral nociceptive stimulation, it can be used as an adjuvant to local anesthetic (LA) solution for different kinds of regional anesthesia and analgesia to improve the quality and prolong the duration of the block.[7]

The objective of the study was to compare the impact of perineural dexmedetomidine and Magnesium sulphate on the duration of supraclavicular brachial plexus block in ASA I and II patients undergoing upper extremity surgery.

II. Materials And Methods

Ethical statement: The study was approved by the Institutional Ethics Committee, Patna Medical College and Hospital, Patna, Bihar, India. Written consent was obtained after informing the participants about the nature, scope and risks related to the study.

Methods: This study was conducted at Patna Medical College and Hospital, Patna, Bihar, India between April 2019 and November 2019. Sixty consenting adult patients were included in this double blind, randomized, controlled study. The sampling type was randomized cluster sampling.

Inclusion criteria

Patients of either sex,

ASA I and II physical status,

Between 18 and 60 years of age,

Scheduled for surgery on upper extremity under supraclavicular brachial plexus block

Exclusion criteria

Patient refusal,

Known contraindications to brachial plexus block (coagulopathy, local infection),

Known allergy to bupivacaine, midazolam or dexmedetomidine,

Concomitant use of analgesics or sedatives,

ASA III / IV patients,

History of significant systemic illness,

Failed brachial plexus block.

Preanaesthesia: Preanaesthetic evaluation of all the patients was performed before admission to the ward. All patients were premedicated with oral ranitidine 150 mg and alprazolam 0.25 mg on the night before surgery and were kept fasting for 6 hours prior to surgery.

Intervention plan: On arrival in the operation theatre, routine monitoring in the form of ECG, NIBP, SPO₂ and respiration were instituted and baseline values were noted. Intravenous access was established with 18G intravenous catheter on the dorsum of the non operative hand and infusion of plasmalyte was started.

By use of computer generated random numbers, patients were allocated to one of two groups;

- Gr M: Patients received ultrasound-guided supraclavicular brachial plexus block with 25 ml Ropivacaine 0.5% and magnesium sulfate. 150 mg of Magnesium sulfate is diluted normal saline and make total volume 5ml.(total volume 30 ml)

- Gr D: Patients received ultrasound-guided Supraclavicular brachial plexus block with 25 ml Ropivacaine 0.5% and dexmedetomidine. 100 µg of dexmedetomidine is diluted normal saline and make total volume 5ml.(total volume 30 ml)

Oxygen through face mask was administered @4L/min to all the patients. Patients were positioned for supraclavicular brachial plexus block. After aseptic preparation of the area, supraclavicular brachial plexus block was performed by Ultrasound guided technique.

Blinding: The study drugs were prepared by an independent clinician not involved in the study. The anaesthesiologist performing the block and observing the patient was blinded to the treatment group. Neither the patient nor the attending anaesthesiologist who also collected the data was aware of the group allocation.

Parameters of observation

Block characteristics

1. Onset of motor block: Time from ropivacaine administration to when a modified Bromage score for upper limb of 2 was achieved.

2. Onset of sensory block: Time from ropivacaine administration to when there was complete lack of cold sensation in the surgical field.

3. Duration of motor block: Time interval between onset of motor block to complete regression of the block (Bromage score 0).

4. Duration of sensory block: Time interval between onset of sensory block to restoration of cold sensation.

Motor block was assessed by modified Bromage scale for the upper limb; 0, normal motor function; 1, ability to move only fingers; 2, complete motor block with inability to move elbow, wrist and fingers.

The regression of block was assessed every thirty minutes till complete recovery from motor and sensory block. Other parameters

Heart rate and Mean arterial pressure: Baseline values were noted and thereafter at every 10min interval till the infusion lasted.

Rescue interventions: Rescue interventions were planned for bradycardia, hypotension and pain;

- Bradycardia (<50 BPM): atropine
- Hypotension (<20% of baseline value): mephenteramine.
- Pain: Diclofenac 1mg/kg as rescue analgesic.

Statistical methods

Power analysis

The primary outcome variable was the duration of the sensory and motor block. The secondary outcome variables included haemodynamic parameters. *PASS version 11* software was used for calculation of sample size, with results of prior study [8]. With power of study 80% and alpha error 5%, the sample size came to 24 for each group. Considering drop outs, 30 patients in each group were recruited.

Statistical software:The data was compiled and subjected to statistical analysis using Statistical Package for Social Sciences [SPSS Inc, Version 20.0.Chicago, IL, USA)

Statistical tests:Statistical tests employed were Student's t-test for age, weight, onset and duration of motor and sensory blocks and hemodynamic parameters. Gender and ASA grade data were subjected to Chi-square test. Data is presented as mean±SD. P-value < 0.05 was considered to indicate statistical significance.

III. Results

Sixty five patients were assessed for eligibility. Three patients did not give consent for participation and two was not included due to presence of chronic kidney disease. Sixty patients were enrolled and randomized to either of the two groups; 30 each in the intervention and the comparator groups. Finally, 27 patients in Group M and 26 patients in Group D were analyzed, the rest being excluded due to failed block [Figure 1]

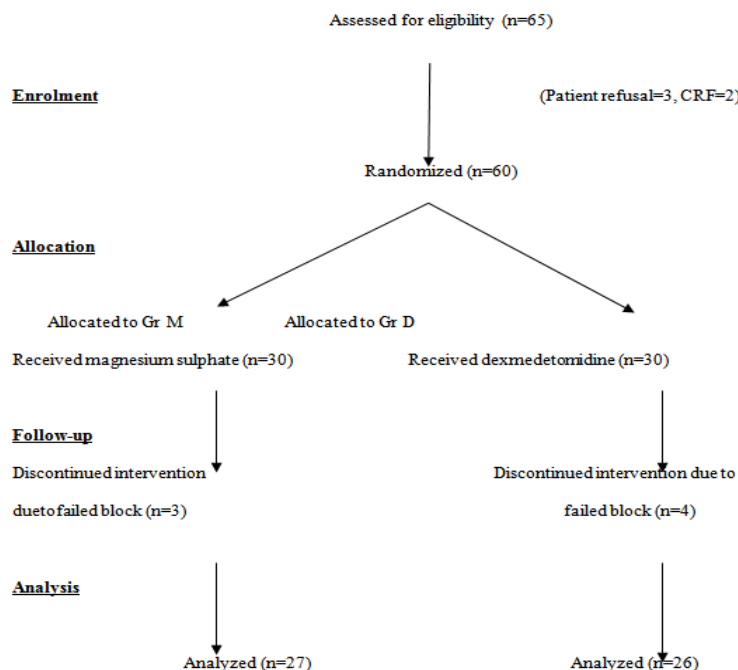


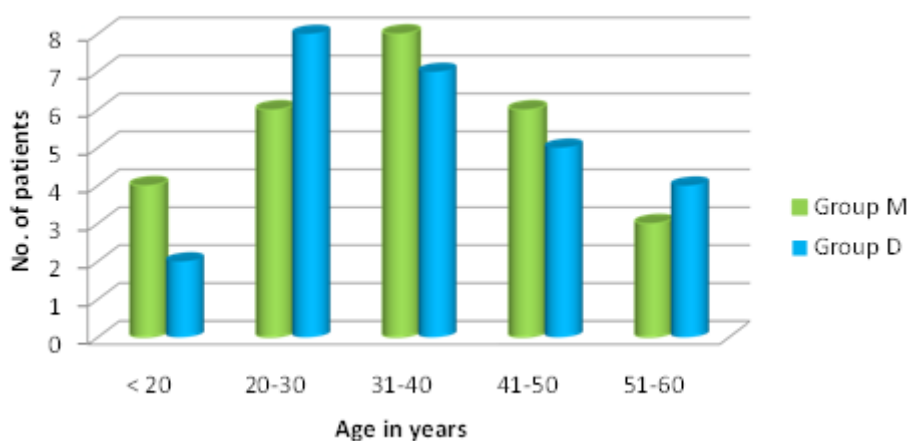
Figure 8. CONSORT flow diagram of study participants

There was no statistically significant difference between the patients in the two groups with respect to age, gender, body weight and ASA physical status [Table 1]. There were 13 male patients in group M whereas group D comprised of 14 males. Eight patients belonged to ASA II status in group M and 6 in group D.

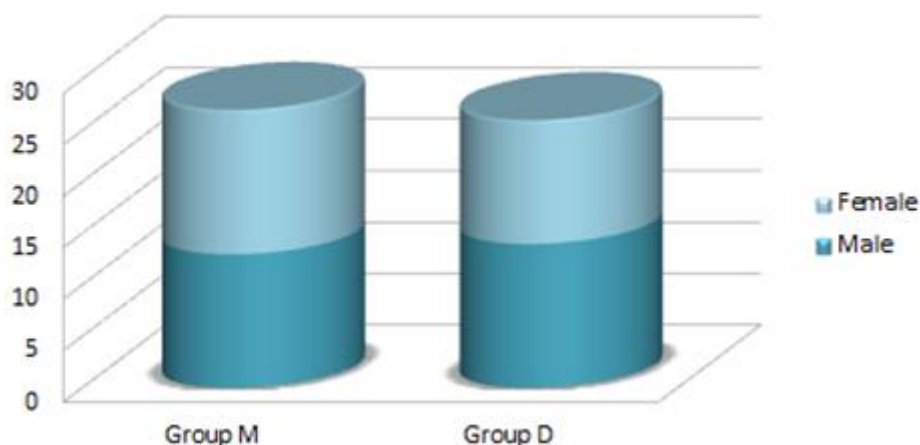
Table 1. Demographic characteristics

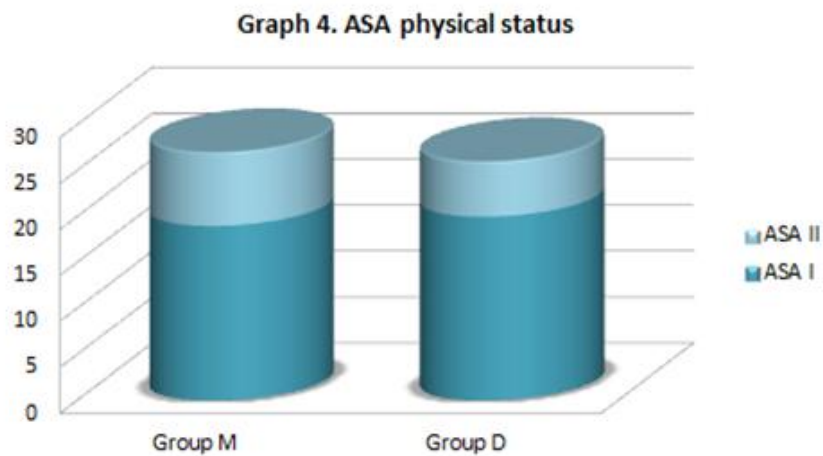
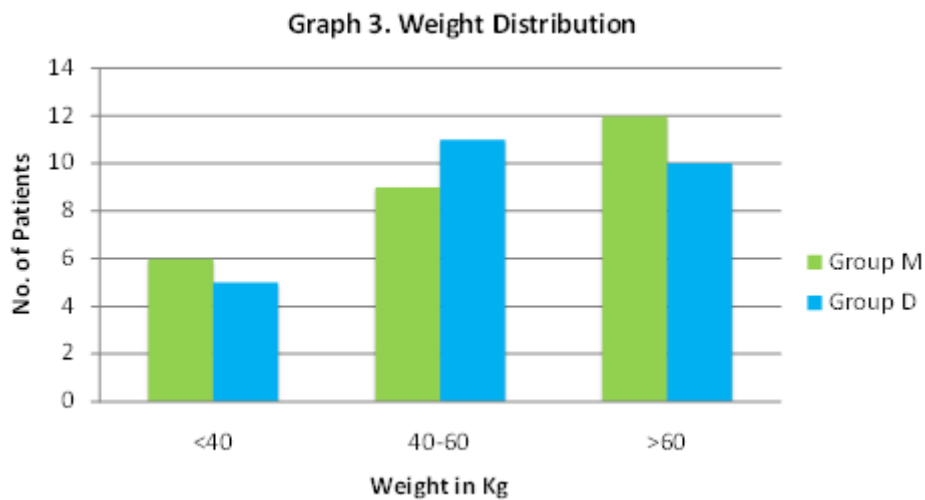
Group M (n=27)	Group D (n=26)		p-value
	Mean±SD	Mean±SD	
Age (Years)	44.3±13.6	39.8±12.3	0.201
Gender (M/F)	14 / 13	12 / 14	0.678
Weight (Kg)	59.7±7.0	56.8±8.4	0.347
ASA grade (I/II)	20 / 7	18 / 8	0.589

Graph 1. Age Distribution



Graph 2. Sex Distribution





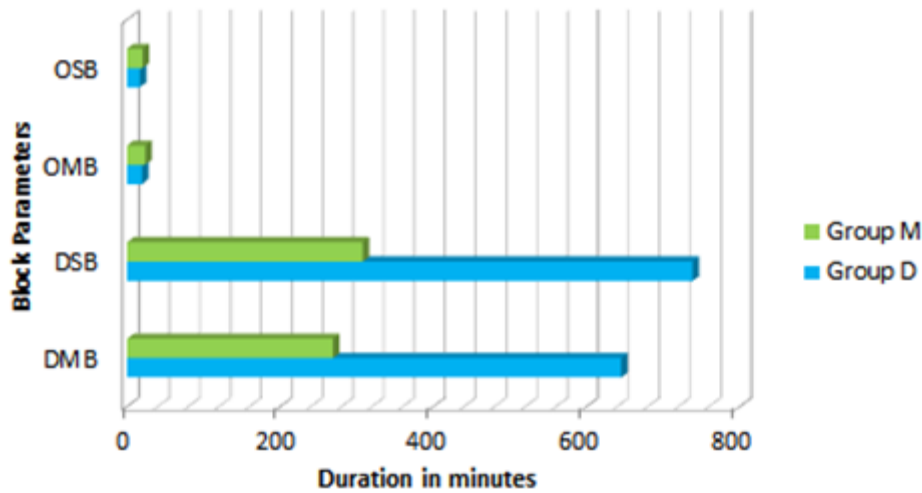
The onset of sensory and motor block was significantly quicker ($p < 0.001$) in group D than in group M [Table 2]. The mean sensory block onset time was 15.6 ± 1.7 minutes in group D as compared to 19.8 ± 1.7 minutes in group M. The mean motor block onset time was 20.5 ± 2.7 minutes in group D when compared to 22.6 ± 1.3 minutes in group M.

The duration of sensory as well as motor block was significantly prolonged ($p < 0.001$) in group D as compared to group M [Table 2]. The duration of sensory block in group D was 788 ± 64.3 minutes where as in group M, it was 317.7 ± 46.7 minutes. The duration of motor block in group M was also prolonged; 695.0 ± 110.0 minutes versus 278.8 ± 32.7 minutes in group M. These differences were highly significant statistically ($p < 0.001$).

Table 2. Block characteristics

	Group M (n=27)	Group D (n=26)	p-value
	Mean \pm SD	Mean \pm SD	
Onset time sensory block (min)	20.5 ± 2.7	15.6 ± 1.7	< 0.001
Onset time motor block (min)	22.6 ± 1.3	19.5 ± 2.7	< 0.001
Duration time sensory block (min)	317.7 ± 46.7	788.4 ± 64.3	< 0.001
Duration time motor block (min)	278.8 ± 32.7	695.0 ± 110.0	< 0.001

Graph 5. Block characteristics



The baseline value of mean arterial pressure was comparable in both the groups [$p > 0.05$] and remained so till the end of the infusion [Table 3].

Table 4. Mean arterial pressure values during the procedure

	Group M	Group D	P value
B	110.19 ± 5.61	99.27 ± 8.62	0.059
10	97.52 ± 5.61	94.88 ± 11.62	0.075
20	98.96 ± 5.94	95.73 ± 13.34	0.440
30	96.56 ± 4.25	94.77 ± 12.09	0.482
40	97.67 ± 5.03	96.62 ± 15.74	0.748
50	97.26 ± 5.71	93.50 ± 14.34	0.222
60	98.81 ± 5.02	95.62 ± 14.46	0.294
70	98.70 ± 5.44	94.36 ± 12.21	0.112
80	99.61 ± 5.87	97.30 ± 9.25	0.344
90	99.88 ± 5.21	96.92 ± 11.30	0.414
100	96.33 ± 3.67	98.29 ± 15.25	0.751
110	97.00 ± 2.00	95.00 ± 1.41	0.285
120		97.00	

MAPB – Baseline mean arterial pressure

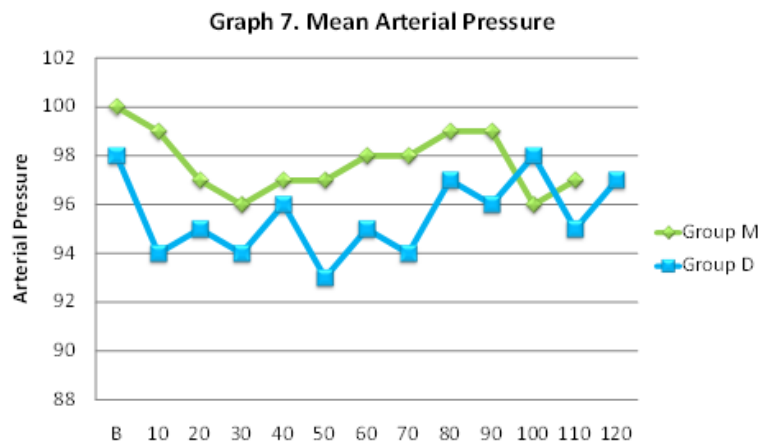
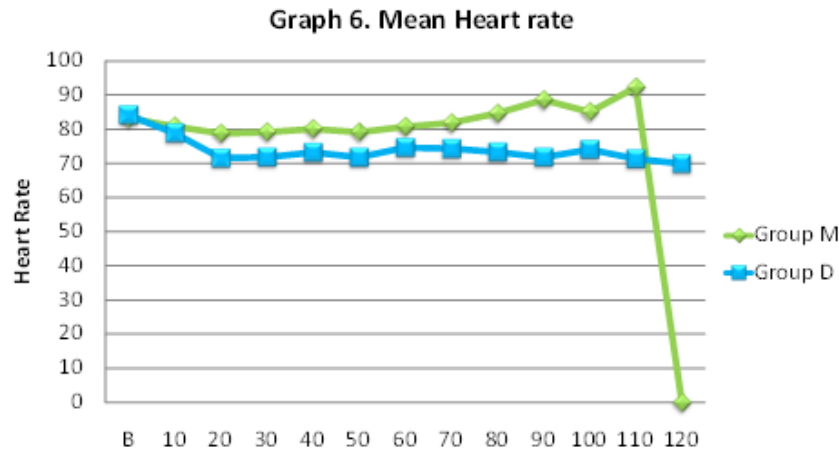
MAP 10 to MAP 120 – Mean arterial pressure after every 10 min interval till 120 minutes

Bradycardia was observed in one patient in dexmedetomidine group that was treated with injection atropine 0.3mg. Hypotension necessitating administration of injection mephentermine 3mg was also observed in one patient in group D [Table 4].

No episode of nausea, vomiting, hypoxemia or respiratory depression was observed in any patient.

Table 4. Adverse events

Group M (n=27)	Group D (n=26)
Bradycardia	0
Hypotension	1



III. Discussion

Prolongation of duration of sensory blockade of ropivacaine for supraclavicular brachial plexus block is beneficial in many ways. It leads to improved postoperative pain management while avoiding opioids or non steroidalanti inflammatory agents. It also helps in avoiding the need for placing catheter for continuous infusion to prolong the block.

Many additives to local anaesthetics have been tried to achieve this goal and some popular options are opioids, dexamethasone, magnesium sulphate and alpha agonists like clonidine and dexmedetomidine.

Synergistic interaction between local and systemic dexmedetomidine and local anaesthetics administered via various routes has been the focus of research for quite some time giving rise to multiple theories.

Alpha-2-agonists act both on pre- and post synaptic sympathetic nerve terminal and central nervous system thereby decreasing the sympathetic outflow and noradrenaline release causing sedative, analgesic, anti-anxiety and sympatholytic effects [9-11].

In animal studies, they have shown to increase the duration of thermal anti-nociception and analgesia [12]. Perineural administration of dexmedetomidine decreases inflammation around peripheral nerves, potentially decreasing peripheral nerve injury [13].

It is known that at the spinal cord level, stimulation of alpha 2 receptors at the substantiagelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P [14]. So, alpha 2-adrenoreceptors located at the nerve endings may have a role in the analgesic mechanism by preventing noradrenaline release. It has been suggested that the spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine even though there is a clear evidence for both supraspinal and peripheral sites of action [11].

The mechanism of the analgesic actions of α -2 agonists is probably multifactorial. A number of supraspinal and spinal sites modulate the transmission of nociceptive signals in the central nervous system. Centrally, they cause analgesia and sedation by activation of α -2 adrenoceptors in the locus coeruleus [15]. Peripheral α -2 adrenoceptors may also mediate antinociception. α -2 agonists by acting at either of these sites reduce nociceptive transmission, leading to analgesia. When added as an adjuvant, it may act directly on the nerve or due to central action after absorption through block site into systemic circulation.

The activation of inwardly rectifying G_1 -protein-gated potassium channels resulting in membrane hyperpolarization and decreasing the firing rate of excitable cells in the central nervous system is considered to be a significant mechanism of the inhibitory neuronal action of α 2-adrenoceptor agonists [16]. Reduction of calcium conductance into cells, thus inhibiting neurotransmitter release is other prominent physiologic action attributed to α 2 adrenoceptors [1]. This effect involves direct regulation of entry of calcium through N-type voltage-gated calcium channels and is independent of cAMP and protein phosphorylation and is mediated by G_0 proteins. These mechanisms represent two different ways of effecting analgesia, that is, the nerve is prevented from firing, and it also prevents propagation of signals to the neighbors. From these observations, it appears that it is the direct peripheral action of dexmedetomidine on nerves, which is responsible for analgesia.

However, the central effects of dexmedetomidine also seems to play some role in prolongation of sensory and motor block duration, as dexmedetomidine intravenous infusion has shown to prolonged brachial plexus block duration [1,7]. Multiple theories exist to explain the analgesic properties of α 2 agonists on the peripheral nerve, including a local vasoconstriction, a direct action on the nerve or a systemic effect [17, 18,19]. The peripheral vasoconstrictive effect of intravenous dexmedetomidine has been investigated in isolation from its sympatholytic effects [19]. Even after denervating the sympathetic nervous activity of the upper limb vasculature by brachial plexus block, vasoconstriction could be observed. This effect, probably, was due to systemic dexmedetomidine. At the same time local activity also plays an important part in prolonging the duration, by prolonging the absorption of local anaesthetic in to the vascular compartment. Based on these observations, we can safely conclude that both central and peripheral mechanism were in play in our patients resulting in prolongation of the block.

However, further investigations including blood levels of α 2 agonists are warranted to investigate the mechanisms of how dexmedetomidine prolongs the action of local anaesthetics in peripheral nerve blocks.

The main findings of this study are that perineurally administered dexmedetomidine; (a) shortens the onset of motor and sensory block, (b) prolongs the duration of motor and sensory block, and (c) does not cause any significant side effect..Seven out of sixty patients were not evaluated due to block failure.

There are very few similar studies and all except one seem to have results identical to ours. In a randomized, controlled study, Kathuria et al evaluated dexmedetomidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block [1]. Addition perineural and coadministration intravenously of dexmedetomidine led to decrease in onset time and increase in duration of motor and sensory blockade. The onset of sensory and motor block in the control group were 22.2 ± 8.62 and 39.05 ± 6.38 minutes respectively as compared to 14.55 ± 8.39 and 30.15 ± 14.52 minutes respectively in the dexmedetomidine sedation group. They observed that these effects were more prominent in patients who had received dexmedetomidineperineurally. Their conclusion, therefore, was that the action of dexmedetomidine is probably local rather than centrally mediated. However, they administered dexmedetomidine infusion over fifteen minutes only unlike in our study where it was administered perineural. Just like in our study, there were no significant side effects like excessive sedation, hypotension or bradycardia.

Agarwal et al evaluated the effect of perineuraldexmedetomidine added to 0.325% bupivacaine compared to bupivacaine solution with normal saline [20]. Perineuraldexmedetomidine as an adjuvant significantly shortened the onset and prolonged the duration of sensory and motor blockade.

Dexmedetomidine causes a transient hypertensive response with doses between 1-4 μ g/kg due to initial stimulation of alpha-2B subtype receptors in vascular smooth muscles. This leads to a reflex bradycardia which persists subsequently due to central sympathetic inhibition [20]. Baroreceptor reflex and heart rate response to pressor agents is preserved. That is why bradycardia and hypotension are easily treatable conferring hemodynamic stability [20].

Hemodynamic parameters in both the groups were compared at an interval of 10 minutes during sedative infusion. The baseline values of mean heart rate were comparable but were found to be significantly lower in the dexmedetomidine group after 20 minutes of infusion. The baseline value of mean arterial pressure

was comparable in both the groups and remained so till the end of the infusion. Bradycardia and hypotension were observed in one patient each in dexmedetomidine group that required treatment.

Previous studies had been investigated the use of magnesium sulfate as an adjuvant to LA solutions for PNB.[21,22] Analgesic effects of magnesium sulfate on the peripheral nerve (PN) may be explained by the NMDA receptors antagonist effect that causes prevention of central sensitization from peripheral nociceptive stimulation,[21] as well as magnesium reduced release of acetylcholine through the competitive block of the calcium entry in presynaptic endings. Another possible mechanism for the action of magnesium sulfate on the PN is the surface charge theory.[21] The modulation of the external magnesium concentration bathing a nerve bundle can enhance the PNB caused by LA, as well as the high concentration of magnesium attracted by the negative charges of the outer membrane surface affected Na⁺ channel gating and could cause hyperpolarization which results in inhibition of nerve conduction.[23] Mukherjee *et al.*[24] studied the effects of using 150 mg magnesium sulfate as an adjuvant to ropivacaine 0.5% for supraclavicular BPB in 100 patients undergoing forearm and hand surgeries. They concluded that the addition of magnesium sulfate to ropivacaine 0.5% resulted in prolongation of the SB and MB durations and the time for the first analgesic request as well as decreased total analgesic consumption without side effects. Haghghi *et al.*[25] in their study on 60 patients undergoing orthopedic surgery of the upper extremities concluded that the addition of 3 mL of 20% magnesium sulfate to lidocaine (5 mg/kg) lengthened the duration of MB and SB of the axillary BPB. Lee *et al.*[21] proved that the use of 2 ml of magnesium sulfate (10%) as an adjuvant to bupivacaine 0.5% with epinephrine (1:200,000) for the interscalene nerve block in 66 patients underwent arthroscopic rotator cuff repair increased the duration of analgesia and reduced the postoperative pain. The favorable effects of magnesium sulfate when added to the LA solution on the improvement of the quality of the regional anesthetic technique, such as i.v. regional anaesthesia, spinal anaesthesia and epidural anaesthesia. On the other hand, Choi *et al.*[26] demonstrated that magnesium sulfate (200 mg) added to ropivacaine 0.2% for axillary BPB in 38 patients undergoing upper extremity surgery reduced neither the level of postoperative pain nor the need for the postoperative opioid.

Our results are consistent with the pharmacological profile of magnesium sulphate and dexmedetomidine and similar to other studies. No episode of nausea, vomiting, hypoxemia or respiratory depression was observed in any patient.

Our study confirms that the onset is shortened and the duration is prolonged of both sensory and motor blockade induced by coadministration of dexmedetomidine during ropivacaine brachial plexus block in ASA I and II patients.

However, the limitations of this study were that the sample size was relatively small and the plasma levels of dexmedetomidine was not measured that could have settled the issue of central versus peripheral action of the drug.

IV. Conclusions

Magnesium sulfate or dexmedetomidine is a useful adjuvant to ropivacaine for Supraclavicular BPB in lengthening the duration of analgesia. Dexmedetomidine provided quicker onset time and longer durations of SB and MB and longer duration of analgesia with lesser requirement of rescue analgesia.

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