Research Paper

Magnesium Sulfate versus Clonidine As an Adjuvant to Ultrasound-Guided Supraclavicular Brachial Plexus Block in Upper Limb Surgery: A Double-Blind Randomized Controlled Trial

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Abstract

Objective: To compare the efficacy of clonidine and magnesium sulfate ($MgSO_4$) when administered as an adjuvant to supraclavicular brachial plexus block in upper limb surgery. **Materials and Methods:** Sixty patients belonging to the American Society of Anesthesiologists classification (ASA) 1 and 2 undergoing upper limb surgical procedures were randomized to receive either 30 μg injection clonidine or 200 mg injection $MgSO_4$ added to 18 ml of 0.5% levobupivacaine + 7 ml of 2% lignocaine with adrenaline. The primary objective of the study was to compare the duration of sensory (postoperative analgesia) and motor block between the two groups. The secondary objectives were to compare the onset time of motor and sensory block along with heart rate and mean arterial pressure between the two groups, which was recorded at regular intervals by the blinded anesthesiologist intraoperatively. Unpaired Student's *t*-test and repeated-measures analysis of variance were used for the analysis of parameters between the two groups. **Results:** There was no statistically significant difference between clonidine and $MgSO_4$ groups in terms of primary outcome, i.e., the duration of postoperative analgesia (12.10 ± 3.86 h vs. 10.93 ± 3.68 h, $P = 0.236$) or duration of motor block (10.67 ± 3.70 h vs. 9.50 ± 2.89 h, $P = 0.180$). The mean onset time for motor block was relatively faster in clonidine group compared to $MgSO_4$ with a borderline significance ($P = 0.049$). No clinically significant difference was observed in the mean onset of sensory block or hemodynamics between the two groups. **Conclusion:** Both, clonidine and $MgSO_4$, as an adjuvant to supraclavicular brachial plexus block were found to have a similar onset time and duration of analgesia and motor block.

Keywords: Adjuvants, brachial plexus, clonidine, levobupivacaine, ultrasound

Introduction

Brachial plexus blocks are the most commonly preferred technique for a number of upper limb surgeries like orthopedic and reconstructive surgeries. Although brachial plexus block is superior to general anesthesia (GA) in terms of reduced hemodynamic instability, avoidance of airway instrumentation, and reduced postoperative pain, the limited duration of action of various local anesthetics continues to be a matter of concern for the anesthesiologist.[1] A variety of perineural adjuvants such as neostigmine, dexamethasone, midazolam, and ketamine have been used to prolong the duration of the block with varying degrees of success and minimal side effects.[2]

Clonidine, an α2 adrenergic agonist, has been used to reduce onset, improve efficacy, and prolong the duration of analgesia when used as an adjuvant in the regional block. However, incidences of bradycardia and excessive sedation have been

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Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_98_20

How to cite this article: Mohanakumar A, Thangavelu R, Paul AA, Ranjan RV, George SK. Magnesium sulfate versus clonidine as an adjuvant to ultrasound-guided supraclavicular brachial plexus block in upper limb surgery: A double-blind randomized controlled trial. J Pharmacol Pharmacother 2020;11:107-12.

Received: 11-06-2020 **Revised:** 01-09-2020
Accepted: 03-10-2020 **Web Publication:** 23-12-2020

reported, especially with the use of high doses.[3] In recent years, there has also been a surge in interest in $MgSO_4$ as an adjuvant to peripheral nerve blocks due to its synergistic effect on local anesthetics.[4] However, there is limited evidence in the literature regarding the comparative efficacy of clonidine and $MgSO_4$ as local anesthetic adjuvants.[5] Hence, we conducted this study to compare the efficacy of $MgSO_4$ or clonidine as an adjuvant to the combination of levobupivacaine, lignocaine and adrenaline in ultrasound-guided supraclavicular block in patients undergoing upper limb surgical procedures.

Materials and Methods

The study was a randomized double-blind controlled trial conducted on 60 patients aged 18–60 years belonging to ASA 1 and 2 undergoing upper limb surgery under ultrasound-guided supraclavicular brachial plexus block in the department of anesthesiology in a tertiary care hospital for a period of 18 months from October 2017 to April 2019. [Figure 1] Clinical Trials Registry – India (CTRI) registration has been obtained for the study. (CTRI registration no. CTRI/2019/04/018780). Patients with preexisting peripheral neuropathy, known neuropsychiatric disorder, local anesthetic hypersensitivity, bleeding disorder, or on anticoagulant therapy with deranged coagulation profile were excluded from the study.[Figure 1] After obtaining ethical committee clearance from the institute (Ref no. IEC: RC/17/60), the study was initiated. All the patients undergoing surgery signed informed written consent and were premedicated with tablet ranitidine 150 mg, tablet lorazepam 2 mg, and tablet perinorm 10 mg in the previous night and the morning of surgery. After transferring the patients to the operation theater, baseline parameters were recorded with ASA standard monitors and an intravenous line was secured. The patients were then divided into two groups based on a computer-generated randomization chart.

- Group A: 18 mL of 0.5% of levobupivacaine + 7 mL of 2% lignocaine with adrenaline and 30 μg of clonidine in 1.8 mL of normal saline (total volume: 27 mL)
- Group B: 18 mL of 0.5% levobupivacaine + 7 mL of 2% lignocaine with adrenaline + 200 mg of magnesium sulfate ($MgSO_4$) in 2 ml of normal saline (total volume: 27 mL).

The primary anesthesiologist blinded to the assignments administered the block under aseptic precautions after positioning the patient supine with the neck turned to the opposite side. Under ultrasound guidance with SonoSite M-Turbo high-frequency linear probe (6–13 MHz), brachial plexus was identified and after confirmation of the needle tip with hydrodissection, the study drug was administered. Once

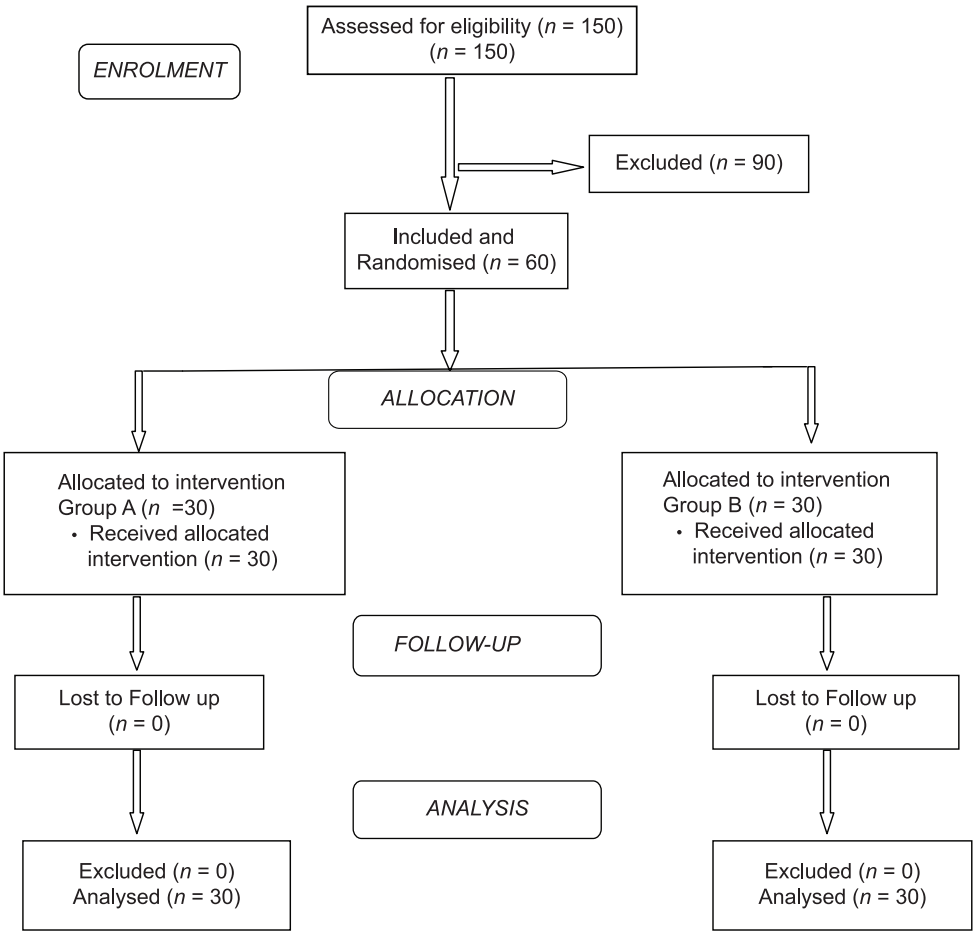

Figure 1: CONSORT diagram showing enrollment, allocation, and analysis at every stage of randomized control trial. *n* = number of patients

the block was administered, the blinded anesthesiologist recorded the onset time for sensory block, onset of motor block, and hemodynamic parameters intraoperatively.

The onset of sensory block was assessed by checking for pain by pinprick test every 5 min in the dermatomal areas corresponding to the median nerve, radial nerve, and ulnar nerve till complete sensory blockade was achieved. Sensory block was graded similar to a previous study as.[6]

- Grade 0: Sharp pain felt
- Grade 1: Dull sensation felt, analgesia
- Grade 2: No sensation felt, anesthesia.

Achievement of Grade 1 block was considered as the time point for the onset of sensory block and Grade 2 as a complete sensory block.

Motor block was graded as:[7]

- Grade 0: Normal motor function with a full range of flexion and extension at the elbow joint, wrist joint, and fingers
- Grade 1: Reduction in motor function with the ability to move fingers only
- Grade 2: Complete motor weakness with absent finger mobility.

Achievement of Grade 1 was considered as the time point for the onset of motor block and Grade 2 as a complete motor block.

Heart rate (HR), blood pressure (mean arterial pressure [MAP]), and saturation (SPO_2) were recorded every 5 min for the first 30 min and then every 15 min till the completion of surgery.

The block was considered partial/incomplete when any one of the segments supplied by median, radial, or ulnar nerve did not have a complete loss of sensation (Grade 2 sensory block) even after 30 min of injection of the study drug. Injection fentanyl 1 mcg/kg was administered intravenously as the rescue drug and reassessed for pain after 10 min. GA was administered in case of no loss of sensation or incomplete loss of sensation even after administration of rescue analgesic and was recorded as a failed block and hence excluded from the study.

Postoperatively, the patients were monitored in the postanesthesia care unit (PACU) for 24 h and the duration of postoperative analgesia and the duration of motor block were recorded by a blinded anesthesiologist.

Visual analogue scale (VAS) was used to assess the duration of analgesia every 30 min with VAS 0 being no pain and VAS 10 having the worst pain. Duration of analgesia was defined as the time from the onset of Grade 1 sensory block till the point where the patient complains of pain (VAS > 3).

Duration of motor block was defined as the time from the onset of Grade 1 motor block till complete return of motor function with adduction of the shoulder, flexion of the forearm, and hand against gravity.

We looked for complications such as hematoma, block failure, pneumothorax, neuropraxia, and bradycardia intraoperatively and during the postoperative period for 24 h.

Patient's demographic and clinical parameters were recorded. Mean ± standard deviation was used to express the continuous variables. The data were tested for normality using Kolmogorov– Smirnov test. Repeated-measures analysis of variance was used to compare the hemodynamic parameters (HR, SpO_2, and MAP) over various time intervals. The onset time and duration of motor and sensory block were compared between the groups using the Student's unpaired *t*-test. All statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) software version 20 (IBM Corp., Armonk,NY, USA) at a 5% level of significance and $P < 0.05$ was considered as statistically significant.

The calculation of sample size was derived from the effect of adding $MgSO_4$ or clonidine to local anesthetic solutions on the duration of analgesia. Based on the results of previous reported studies,[4,8] 25 patients were required to detect a significant difference in the duration of analgesia of 45 min at an alpha error of 0.05 and power of 80%. We included 30 patients in each group to allow for withdrawal or drop out due to any reasons.

Results

A total of 60 patients were enrolled in the study, with 30 patients in each group.

The two groups had comparable baseline characteristics of age, gender, weight, and ASA class [Table 1].

The mean onset time for sensory block was 5.40 ± 3.058 min and 7.47 ± 5.329 min in clonidine and $MgSO_4$ group, respectively (P = 0.072). The onset of motor block was relatively faster with the clonidine group as compared to the $MgSO_4$ group with a borderline significance (8.30 ± 3.303 min and 10.80 ± 5.910 min, respectively, P = 0.049) [Table 2].

There was no overall statistically significant difference between the two groups with regard to HR, MAP, and SPO2 [Figures 2 and 3].

The patients were followed up postoperatively every 30 min to assess for the total duration of motor block and duration of postoperative analgesia using the VAS score. The mean duration of analgesia was 12.10 ± 3.863 h and 10.93 ± 3.685

Table 1: Comparison of patient characteristics among the two groups

Parameter	Group A (n=30)	Group B (n=30)
Age (years), mean±SD	35.03±12.40	34.43±11.44
Weight (kg), mean±SD	68.63±13.83	68.93±10.49
Gender (male/femlae), *n*	25/5	22/8
ASA (I/ II), *n*	20/10	24/6

Data presented as mean±SD, except for gender. *n*=Number of patients, SD=Standard deviation, Group A=Clonidine, Group B=$MgSO_4$, ASA=American Society of Anesthesiologists

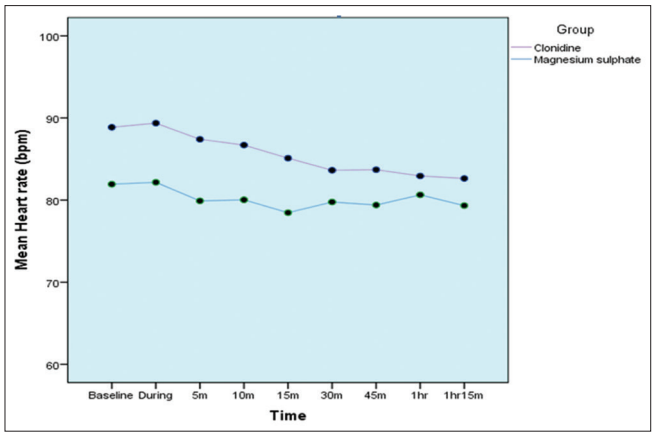

Figure 2: Comparison of heart rate between the two groups. Heart rate was comparable between the two groups at various time points

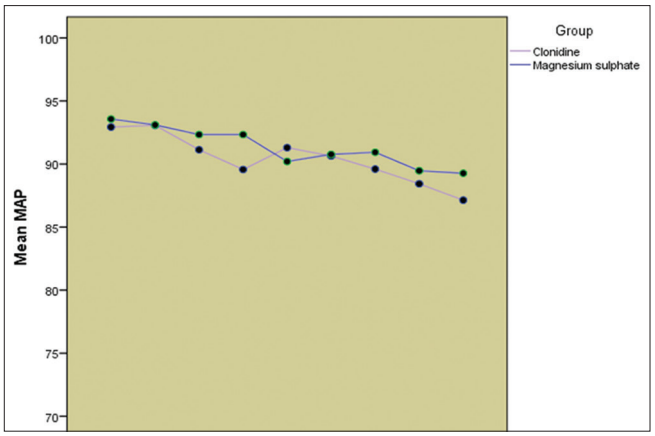

Figure 3: Comparison of mean arterial pressure (mm Hg) between the two groups at various time points

Table 2: Comparison of block characteristics among the two groups

Parameter	Mean±SD		*P*
	Group A (*n*=30)	Group B (*n*=30)	
Onset of sensory block (min)	5.40±3.05	7.47±5.32	0.072
Onset of motor block (min)	8.30±3.30	10.80±5.91	0.049*
Duration of analgesia (h)	12.10±3.86	10.93±3.68	0.236
Duration of motor block (h)	10.67±3.70	9.50±2.89	0.180

*Statistically significant. Data presented as mean±SD. *n*=Number of patients, SD=Standard deviation, Group A=Clonidine, Group B=$MgSO_4$

h in clonidine and $MgSO_4$ group respectively (P = 0.236). There was no statistically significant difference in the mean duration of motor block between the two study groups postoperatively (P = 0.180) [Table 2].

Due to partial block, one patient in clonidine group and three patients in the $MgSO_4$ group received fentanyl as rescue analgesia. None of the study participants had block failure or required GA. There was no incidence of any hematoma, pneumothorax, neuropraxia, or somnolence noted in any of the patients during the study.

Discussion

Brachial plexus block is a frequently used regional anesthesia technique that provides several advantages in terms of excellent pain control, reduced side effects, and shortened stay in the PACU. The commonly used bupivacaine is being replaced by levobupivacaine, a racemic S enantiomer of bupivacaine, mainly because of its less cardiotoxic effects.[9] Several adjuvants, namely midazolam, ketamine, dexamethasone, and dexmedetomidine are added to improve the efficacy as well as extend the duration of postoperative pain relief with local anesthetics.[10,11]

Clonidine, an alpha 2 adrenergic agonist, when administered as an adjuvant, has been found to improve the quality of anesthesia and analgesia in peripheral nerve blocks.[12] This is thought to be due to its centrally mediated analgesia by its action on alpha 2 receptors on the dorsal horn, vasoconstriction, anti-inflammatory, and its direct effects on A and unmyelinated C fibers (increases the conductance of potassium, thereby producing hyperpolarization).[7]

Many have focused on the effect of clonidine as an additive to local anesthetic in doses using 2–3 μg/kg, a moderately high dose with its attendant risk of adverse drug reaction.[3,8] In a study done by Kohli *et al*.,[13] two doses of clonidine (1 μg/kg compared to 2 μg/kg) were studied as an adjuvant in the supraclavicular block with 30 mL of 0.5 bupivacaine. Although the onset time of motor block and duration of motor block were significantly faster and longer (13.2 vs. 18.5 min and 21.0 vs. 14.9 h, respectively) with the higher dose, it was found to have significant sedation, hypotension, and bradycardia among the groups receiving the higher dose.

Since the average Indian population has relatively lower body weight and since there are limited studies with low dose of clonidine, we selected a dose of 30 μg to be administered as an adjuvant to levobupivacaine. It was found that the dose provided satisfactory prolongation of postoperative analgesia (12.10 ± 3.86 h) without producing significant hemodynamic compromise in these patients. The results were similar to a study done by Chakraborty *et al*.[14] who did a randomized control trial to study the effect of 30 μg clonidine as an adjuvant to supraclavicular block. They found that the onset of both sensory (6.2 min vs. 8.7 min) and motor blocks (10.6 min vs. 18.1 min) was significantly faster in the group receiving clonidine as compared to the placebo. The total duration of analgesia was about 415.4 ± 38.18 min.

$MgSO_4$ has been used as an antihypertensive, analgesic, and as an anesthetic sparing agent under both general and regional anesthesia. Many clinical studies have concluded that $MgSO_4$ used during GA decreased the anesthetic requirements and the need for postoperative rescue analgesics.[15,16] Recently, it is also being used as an adjuvant in peripheral nerve blocks because of its antinociceptive properties.[4] The mechanism can

be explained by inhibition of calcium entry into the cell and antagonism of N methyl D aspartate (NMDA) receptors. Various studies in the literature support the findings of faster onset and long duration of a block with varying doses of $MgSO_4$.[17]

Lee et al. found that the addition of 2 mL of 10% $MgSO_4$ (200 mg) to a 0.5% bupivacaine epinephrine mixture for an interscalene nerve block prolonged the duration of analgesia from 553 ± 155 min to 664 ± 188 min. and thus reduced postoperative pain in orthopedic shoulder procedures with no recorded adverse effects.[18] The results were similar to our study where we used a similar dose (200 mg) of $MgSO_4$ as an adjuvant and found a prolonged duration of analgesia of 10.93 ± 3.685 h postoperatively.

In a study by Rana et al., $MgSO_4$, when added as adjuvant was found to shorten the onset of the block (5.17 ± 2.2 min vs. 8.9 ± 2.3 min) and extend the duration of analgesia (665.13 ± 97.874 vs. 475.10 ± 53.294 min) in a dose-dependent manner with a dose of 250 mg having a greater efficacy compared to 125 mg without any adverse effects or reported neurotoxicity.[19]

The majority of previous studies have used clonidine and $MgSO_4$ as the study drug in comparison to placebo and established their analgesic efficacy when used as local anesthetic adjuvants.[20] However, studies with head-to-head comparisons of $MgSO_4$ and clonidine as an additive to local anaesthetic in peripheral nerve blocks are limited in the literature. One of the studies by Abd el Motlb and Ramzy.[21] evaluated the analgesic and hemodynamic effects of mixing bupivacaine 0.25% with either clonidine (150 μg) or $MgSO_4$ (150 mg) in intercostal nerve block combined with GA for simple mastectomy surgery. The results showed that though clonidine and $MgSO_4$ increased the duration of analgesia individually when compared to saline (487 ± 118 min and 484 ± 122 min respectively vs. 395 ± 125 min), there was no statistically significant difference when compared between the two drug groups. Furthermore, since a high dose of clonidine was used in the study, there was a relative incidence of hypotension and bradycardia during anesthesia and high degree of sedation postoperatively.

The strengths of the study are only a few head-to-head comparison studies of $MgSO_4$ and clonidine available in the literature. Furthermore, the lowest effective doses (as determined in the literature) were used and no adverse effects were recorded in either of the groups.

The limitations were absence of a placebo group in our study. In addition, the degree of sedation was not measured and only any incidence of somnolence was looked for. Further future research in the direction of doses of $MgSO_4$ and clonidine in comparison to placebo might be warranted in a large sample of patients and different surgical settings.

Conclusion

Both clonidine and $MgSO_4$ were found to have a comparable duration of analgesia and degree of motor block postoperatively when used as an adjuvant to the combination of levobupivacaine and lignocaine in brachial block for upper limb surgeries. The drug clonidine had a relatively faster onset of motor block in comparison to $MgSO_4$.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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