Abstract

Background: Supraventricular brachial plexus block offers good operating conditions with limited postoperative analgesia. Magnesium sulfate (MgSO₄) and ketamine block peripheral nociception mediated via N-methyl-D-aspartate receptors. Aims: The aim of this study was to evaluate the effect of MgSO₄ and ketamine on the duration of analgesia in brachial block. Settings and Design: This was a prospective, randomized, controlled double-blind study. Materials and Methods: One hundred and five adult patients were randomly divided into three groups: Group I = 27 mL of 0.5% ropivacaine; Group II = 27 mL of 0.5% ropivacaine + 250 mg MgSO₄; and Group III = 27 mL of 0.5% ropivacaine + 2 mg.kg⁻¹ ketamine. Normal saline was added to make a total volume of 30 mL. The onset and duration of the sensorimotor blockade, quality and duration of postoperative analgesia, and adverse effects were assessed. Statistical Analysis: Statistical analysis was performed using SPSS, version 17.0 software (SPSS, Inc., Chicago, IL, USA). Chi-square test was used for nonparametric and ANOVA for parametric data. Post hoc Student’s paired t-test was applied wherever indicated. The results were expressed as mean and standard deviation or numbers (%). P < 0.05 was considered as statistically significant. Results: The duration of analgesia was significantly longer in Group II (8.78 ± 0.97 h) compared to Group I (6.76 ± 0.92 h; P < 0.001) and Group III (7.1 ± 0.89 h; P < 0.001). Intervention groups had lower postoperative visual analog scores at 8, 12, and 24 h compared to the control group. Sedation, nystagmus, and hallucinations were observed in Group III. Conclusion: The addition of MgSO₄ to ropivacaine in supraventricular brachial plexus block significantly prolongs the duration of analgesia. MgSO₄ improves the quality of postoperative analgesia with lesser incidence of side effects when compared to ketamine.

Keywords: Analgesia, ketamine, magnesium sulfate, ropivacaine, supraventricular brachial plexus block

Introduction

Supraventricular brachial plexus block is a safe and inexpensive anesthetic technique for upper limb surgeries offering good operating conditions along with the advantage of postoperative analgesia.¹ Since the duration of postoperative analgesia is often a limiting factor, many adjuvants, such as tramadol, morphine, fentanyl, epinephrine, α₂ agonists, dexamethasone, neostigmine, midazolam, ketamine, and sodium bicarbonate, have been used along with local anesthetics to this end.²⁻⁵ These are often associated with adverse effects, and the results have been inconclusive.⁶

An understanding of pain mechanisms points to the role of central sensitization and N-methyl-D-aspartate (NMDA) receptor activation by excitatory amino acid transmitters in postsurgical pain.⁷⁻⁹ Magnesium sulfate (MgSO₄), an NMDA receptor antagonist in the central and peripheral nervous system, has been evaluated as an adjuvant in the perioperative analgesic management and was found to decrease the intraoperative and postoperative analgesic consumption.¹⁰⁻¹³ Some authors also suggest a prolonged duration of analgesia when used as an adjunct to different local anesthetics.¹⁴,¹⁵ However, in vivo, MgSO₄ was shown to shorten the effects of amide local anesthetics on the rat sciatic nerve.¹⁶

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Ketamine is also a noncompetitive NMDA receptor antagonist commonly used for its analgesic and anesthetic effect. It also possesses central, regional, and local anesthetic properties, and recent clinical applications include its use as an adjunct in caudal or Bier’s block. It has also been used in pectoral nerve block, axillary block, and supraclavicular block with contradicting results.

Both these drugs have been used in combination with different local anesthetics for perineural injections, but the results are inconclusive, and no concrete recommendation for their use as adjuvants exists at present. In addition, available data on direct comparison of the two NMDA receptor antagonists in the supraclavicular block are limited. Hence, the present study aimed to evaluate the effect of MgSO₄ compared to ketamine when added to 0.5% ropivacaine for supraclavicular brachial plexus block, in terms of the duration of postoperative analgesia in adult patients undergoing upper limb surgery. The effect of the study drugs on the onset and duration of sensorimotor blockade was also assessed.

Materials and Methods

This prospective, randomized, double-blind study was conducted at a tertiary care teaching hospital in North India. The study was approved by the hospital ethics committee (Ref. No.Patho94/17, dated: February 6, 2017) and registered with Clinical Trials Registry, India (www.ctri.nic.in). Prior informed written consent was obtained, and individuals were enrolled from February 2017 to August 2018. A total of 105 adult patients (20–60 years) of either sex, American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective upper limb surgery (forearm and hand) were included. Patients with peripheral neuropathy or motor weakness, infection at the injection site, pneumothorax, diaphragmatic paralysis, known allergy to the drugs used, bleeding disorders, uncooperative, or not able to understand the visual analog scale (VAS) were excluded from the study. A sample size of 93 was calculated to determine the difference in the primary outcome variable (duration of analgesia) at 95% confidence interval, 5% alpha error, and the power of the study 90%. It was increased by 10% to a total of 105, to make up for dropouts or failures.

Preoperative assessment including a detailed history and general and systemic examination was performed a day before surgery. Patients were weighed, and routine laboratory investigations were done. The study protocol, procedure of brachial plexus block, and VAS (0–10) was explained to the patient, and an informed written consent was obtained. All the patients were given tablet alprazolam 0.5 mg orally the night before surgery and were kept fasting overnight.

The patients were reassessed in the preoperative holding area and randomly assigned to one of the three study groups according to computer-generated random number slips enclosed in 105-sealed opaque envelopes. To conceal the group allocation, the sealed envelope was opened just before the block performance. To ensure blinding, an independent anesthesiologist not involved in the data collection prepared the drug solution according to the assigned group. Group I patients received 27 mL of 0.5% ropivacaine alone, Group II patients were given 27 mL of 0.5% ropivacaine with MgSO₄ (250 mg), and for patients in Group III, ketamine (2 mg.kg⁻¹) was added to 27 mL of 0.5% ropivacaine. Normal saline was added to all the solutions to make a total volume of 30 mL. The procedure was performed by another anesthesiologist who was not aware of the composition of the drug solution. The person recording the observations and the patients were also unaware of the group allotment and drugs used.

In the operating room, intravenous (i.v.) access was secured and injection midazolam 0.5–1 mg was given. Heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SpO₂) were recorded at the baseline and then every 15 min till the end of the surgery. Supraclavicular brachial plexus block was performed using a peripheral nerve stimulator (Stimuplex® HNS 12, B. Braun Melsungen AG, 34209 Melsungen, Germany), and the drug solution was injected as per the group allocation.

Sensory block assessment was done on a 4-point scale (1 – full sensation [sharp, same as control area]; 2 – weak sensation [sharp, less than control area]; 3 – light touch [can feel something, but not sharp]; and 4 – no sensation) in the distribution of median, radial, ulnar, and musculocutaneous nerves, every 2 min for 20 min after drug injection. The sensory block of Grade ≥3 was considered acceptable for surgery to proceed, and the time taken to achieve this was taken as the onset of sensory block.

Motor blockade was evaluated using a 3-point scale (Grade 0 – normal motor function, ability to move arm; Grade 1 – decreased motor strength with ability to move fingers only; and Grade 2 – complete motor block with inability to move elbow, wrist, and fingers). The onset of motor block was taken as the time elapsed between drug injection and development of complete motor block (Grade = 2). The block was considered inadequate if a patient moved the arm or felt pinprick sensation even after 30 min of performing block. Single nerve sparing was treated with local infiltration or peripheral nerve block. Sparing of more than one nerve was treated with midazolam (0.05 mg/kg), total i.v. anesthesia (TIVA) with propofol, or general anesthesia with endotracheal intubation, and these cases were excluded from the statistical evaluation.

Sensory and motor blockade was assessed hourly till the complete block resolution. Time elapsed between the injection of drug and return of pinprick sensation (Grade = 2) and complete return of motor power (Grade = 0) were, respectively, taken as duration of sensory and motor block.

Quality of postoperative analgesia was evaluated at 2, 4, 6, 8, 12, and 24 h after the surgery using the VAS (0–10, 0 = no pain and 10 = worst pain imaginable). Rescue analgesia in the form of injection diclofenac 75 mg i.v. was given on patient’s demand. Duration of analgesia was defined as the time from the performance of block to the first rescue analgesic. Any...
procedure-related complications such as pneumothorax, hematoma, postoperative paresthesia or excessive sedation, nausea, and vomiting were taken note of and treated.

Side effects such as bradycardia (HR <50/min), hypotension (reduction of MAP ≥20% of the baseline or an absolute MAP ≤60), and respiratory depression (respiratory rate ≤8 breaths/min or SpO₂ <94%) were treated, respectively, with atropine i.v. bolus of 0.6 mg, i.v. crystalloid boluses or mephentermine i.v. 3 mg aliquots, and supplemental oxygen.

Statistical analysis
Statistical analysis was performed using SPSS, version 17.0 software (SPSS, Inc., Chicago, IL, USA). Mean and standard deviation were used to represent the average and typical spread of values. The precision of estimates was shown as 95% confidence limits. Categorical data were expressed as frequency (%). Chi-square test was used for nonparametric data and ANOVA for parametric data. Post hoc Student’s paired t-test was applied wherever indicated. P < 0.05 was considered as statistically significant.

Results
A total of 122 patients were assessed for inclusion, of which 12 did not meet the inclusion criteria and 7 patients refused to participate in the study. Of the 105 patients included in the study, 6 patients (1 in Group I, 1 in Group II, and 4 in Group III) required TIVA or general anesthesia due to incomplete block effect [Table 1]. These patients were included in the demographic profile but excluded from the final statistical analysis, for which 99 patients were considered. The three groups were statistically comparable with respect to demographic data (age, sex, weight, and ASA status) and duration of surgery [Table 1].

The difference in the onset of sensory and motor block was statistically insignificant between the groups [Table 2]. The addition of MgSO₄ to ropivacaine significantly prolonged the duration of sensorimotor blockade compared with both ketamine–ropivacaine and ropivacaine alone (P < 0.001). The duration of analgesia was also longer in Group II compared to Group I and Group III (P < 0.001). The difference in the duration of sensorimotor blockade and duration of analgesia between ketamine and control groups was not significant (P > 0.05).

All the patients were pain free for 2 hours. After this period, the patients receiving magnesium had significantly lower postoperative VAS scores compared to control group for 24 h (P < 0.001) [Table 3]. Group III patients also had significantly lower VAS scores at 4, 8, 12, and 24 h postoperatively compared to Group I, but the VAS score at 6 h was comparable. Between the two adjuvants, the use of magnesium was associated with significantly lower VAS at 6, 8, and 12 h postoperatively; however, at 4 and 24 h, they were comparable to patients receiving ketamine (P < 0.05).

All the patients in Group III exhibited mild sedation which was not observed in the other two groups. The incidence of complications (nystagmus and hallucinations) was significantly more with ketamine [Figure 2].

Discussion
The results of the present study demonstrated that the addition of 250 mg MgSO₄ to ropivacaine for supraclavicular brachial plexus block significantly prolongs the duration of postoperative analgesia, as well as the duration of sensorimotor blockade compared to ketamine with ropivacaine and ropivacaine alone. The block characteristics (duration of sensory block, motor block, and analgesia) were not statistically different in ketamine–ropivacaine and ropivacaine groups. Both magnesium and ketamine offered better postoperative analgesia compared to the control group; however, of the two additives, magnesium was associated with significantly lower VAS scores. The adjuvants did not shorten the onset of sensorimotor block. Minor complications such as nausea, hallucinations, and nystagmus were observed in patients given ketamine.

Perineural administration of MgSO₄ prolonged the duration of analgesia and sensorimotor block. Elyazed and Mogahed studied the effects of adding 150 mg MgSO₄ to 0.5% ropivacaine in infraclavicular block and observed significant prolongation of both sensorimotor block and duration of analgesia without any side effects.[22] Mukherjee et al. also reported a longer duration of block and time to the first analgesic request with magnesium.[23] Other authors observed similar results with different doses of MgSO₄ added to different local anesthetics for the brachial block.[24-26] On the contrary, Choi et al. reported no difference in the postoperative VAS and opioid consumption.[27] The discrepancy in the results could be attributed to various differences in the methodology, such as lower concentration (0.2%) and volume (20 mL) of ropivacaine and site (brachial) and timing (postoperative) of block.

Table 1: Demographic profile of the study group patients

| Variables | Group I | Group II | Group III | P  |
|-----------|---------|----------|-----------|----|
|           | Mean ± SD | CI   | Mean ± SD | CI   | Mean ± SD | CI   | I versus II | I versus III | II versus III |
| Age (years) | 38.80±14.37 | 33.86-7.37 | 45.22±11.71 | 41.20-9.25 | 38.34±13.47 | 33.71-4.97 | 0.110 | 0.989 | 0.080 |
| Body weight (kg) | 63.73±5.86 | 61.68-5.78 | 62.79±7.38 | 60.21-6.57 | 63.32±7.11 | 60.71-6.93 | 0.837 | 0.968 | 0.948 |
| Sex ratio (male/female) | 28/7 | 30/5 | 27/8 | 27/8 | 0.649 |
| ASA status (I/II) | 25/10 | 17/18 | 27/8 | 0.029* |
| Duration of surgery (min) | 106.03±16.45 | 100.30-111.77 | 105.44±16.02 | 98.85-111.03 | 105.83±17.96 | 98.07-14.05 | 0.990 | 1.000 | 0.990 |

*Significant, †Data represented as number of patients. ASA=American Society of Anesthesiologists, SD=Standard deviation, CI=Confidence interval
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We did not observe any significant difference in the onset of sensory and motor block, which was consistent with previous studies. However, in contrast with our results, Verma et al. and Dogru et al. observed quicker onset of sensory and motor block when MgSO₄ was added to bupivacaine and levobupivacaine, respectively. The difference could be attributed to the local anesthetics used, indicating variable interaction of magnesium with different local anesthetics.

Ketamine added to ropivacaine did not offer any improvement in block characteristics which were comparable to control group. Senel et al. and Lashgarinia et al. also made similar observations with ketamine as an adjuvant to ropivacaine or lignocaine in brachial plexus block. NMDA receptor antagonists have the potential to obtund the cell’s response to painful stimuli by blocking central sensitization and peripheral nociceptive stimulation. Ketamine is known for its analgesic properties mediated by NMDA antagonism. MgSO₄, also recognized as NMDA receptor antagonist, has been investigated for its antinociceptive and analgesic properties. Perineural administration of magnesium in the axillary sheath had a dose-dependent effect in improving postoperative analgesia. The hypothetical possibility of synergism with local anesthetic drugs has been probed by various authors yielding conflicting results. The effects appear to differ with different local anesthetics.

To the best of our knowledge, there is no systematic review referring to the use of MgSO₄ or ketamine in brachial plexus block.
Table 2: Effect of the study drugs on block characteristics

| Variable                      | Group I (n=34) Mean±SD | Group II (n=34) Mean±SD | Group III (n=31) Mean±SD | CI     | CI     | I versus II | I versus III | II versus III |
|-------------------------------|------------------------|-------------------------|--------------------------|--------|--------|------------|------------|-------------|
| Onset of sensory block (min)  | 15.61±1.39             | 15.13-16.10             | 15.65±1.62               | 15.09-16.21 |        | 0.993       | 0.997       | 0.999       |
| Onset of motor block (min)    | 20.26±1.69             | 19.67-20.85             | 21.11±1.52               | 20.58-21.63 |        | 0.056       | 0.129       | 0.950       |
| Duration of sensory block (h) | 5.35±0.58              | 5.14-5.55               | 7.18±1.02                | 6.83-7.53 |        | <0.001*     | 0.590       | <0.001*     |
| Duration of motor block (h)   | 4.51±0.70              | 5.14-5.55               | 5.67±0.72                | 6.83-7.53 |        | <0.001*     | 0.078       | <0.001*     |
| Duration of analgesia (h)     | 6.76±0.92              | 6.44-7.08               | 8.78±0.97                | 8.44-9.12 |        | <0.001*     | 0.361       | <0.001*     |

*Significant. n=Number of patients, SD=Standard deviation, CI=Confidence interval, Group I=27 mL of 0.5% ropivacaine, Group II=27 mL of 0.5% ropivacaine + 250 mg magnesium sulfate, Group III=27 mL of 0.5% ropivacaine + 2 mg/kg ketamine

Table 3: Effect of the study drugs on analgesia for the first 24 h of postoperative period

| Postoperative duration (h) | Visual analog score (mean±SD) | I versus II | I versus III | II versus III |
|----------------------------|-------------------------------|------------|------------|-------------|
| 0                          | 0.0±0.0                       | 0.0±0.0    | 0.0±0.0    | 0.0±0.0    |
| 2                          | 0.0±0.0                       | 0.0±0.0    | 0.0±0.0    | 0.0±0.0    |
| 4                          | 0.14±0.35                     | <0.001*    | 0.122      | 0.001*     |
| 6                          | 1.71±0.62                     | <0.001*    | 0.014*     | <0.001*    |
| 8                          | 3.54±0.61                     | <0.001*    | <0.001*    | 0.005*     |
| 12                         | 4.80±0.67                     | <0.001*    | <0.001*    | 0.987      |
| 24                         | 6.08±0.61                     | <0.001*    | <0.001*    | 0.005*     |

*Significant. n=number of patients, SD=Standard deviation, CI=Confidence interval, Group I=27 mL of 0.5% ropivacaine, Group II=27 mL of 0.5% ropivacaine + 250 mg magnesium sulfate, Group III=27 mL of 0.5% ropivacaine + 2 mg/kg ketamine

block. The disparity of available evidence would justify a systematic review to guide future recommendations.

The absence of selection bias and blinding at multiple levels were the strengths of this study. We, however, recognize few limitations. Serum levels of the drugs were not measured; thus, it could not be discerned whether the effect of the study drugs was due to systemic absorption or some local mechanism. Including the study groups to compare systemic administration of the study drugs with perineural administration might further clarify this aspect.

**Conclusion**

Both 250 mg MgSO₄ and 2 mg·kg⁻¹ ketamine when added to 0.5% ropivacaine for supraclavicular brachial plexus block improve the quality of postoperative analgesia when compared to ropivacaine alone. However, among the two study drugs (MgSO₄ and ketamine), MgSO₄ proved superior in terms of block characteristics (duration of sensory and motor blockade and duration of analgesia) and lesser incidence of side effects when used as an adjuvant to ropivacaine in supraclavicular brachial plexus block.

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**Conflicts of interest**

There are no conflicts of interest.

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