

# Comparison of intravenous route versus nebulization of magnesium sulfate ( $MgSO_4$ ) for post-operative sore throat and hoarseness: A randomized comparative double-blinded clinical trial



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## ABSTRACT

**Background:** Multiple drugs in different routes have been studied for the treatment of post-operative sore throat (POST). We are studying effect of magnesium sulfate on POST in two different routes. **Aims and Objectives:** This study aims to compare the efficacy of nebulization versus intravenous (IV) magnesium sulfate in reducing incidence of POST and hoarseness of voice. **Materials and Methods:** This prospective randomized double-blind study was done on 150 patients undergoing unilateral percutaneous nephrolithotomy (PCNL) surgeries under general anesthesia. Patients were randomly allocated into Group N (n = 75) and Group I (n = 75). Group N received 10 mg/kg  $MgSO_4$  in 5 mL of normal saline as nebulization 20 min before induction and 100 mL normal saline IV over 20 min post-induction. Group I received 5 mL of normal saline as nebulization pre-induction and 10 mg/kg  $MgSO_4$  in 100 mL saline IV over 20 min post-induction. Postoperatively, visual analog scale (VAS) score was used for the assessment of sore throat at rest and dynamic VAS (DyVAS) for pain during swallowing at the 0, 1<sup>st</sup>, 6<sup>th</sup>, 12<sup>th</sup>, and 24<sup>th</sup> h. Post-operative hoarseness graded on 4-point score was also assessed. **Results:** Incidence of POST in Group N was 29.17% compared to 52.86% in Group I at 0 h which was lower and statistically significant and results were alike at the 1<sup>st</sup> and 6<sup>th</sup> h. The VAS at rest and DyVAS were lower and statistically significant in Group N compared to Group I at the 0, 1<sup>st</sup>, and 6<sup>th</sup> h. **Conclusion:** Incidence of POST was significantly less with nebulized route of magnesium sulfate compared to IV route of magnesium sulfate.

**Key words:** Intravenous; Magnesium sulfate; Intubation; Percutaneous nephrolithotomy; Sore throat

## INTRODUCTION

The trends in field of anesthesiology keep changing rapidly. Any complications during post-operative period can delay recovery and hamper early discharge from hospital. Recent emphasis has been toward early recovery of the patient postoperatively. Multimodal analgesia, mostly after advent of ultrasound-guided peripheral nerve blocks, has helped management of post-operative pain. Due to good surgical site pain, management other discomforts like

post-operative sore throat (POST) can debilitate the patient and cause dissatisfaction.

POST commonly occurs after endotracheal intubation and is regarded as most common complication with incidence varying from 21% to 65%.<sup>1,2</sup> Various pharmacological and non-pharmacological measures have been taken as it can lead to patient discomfort in the recovery period. Non-pharmacological measures such as smaller size endotracheal tubes, smooth laryngoscopy and intubation,

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and designed cuff with optimum pressure were used previously.<sup>3,4</sup>

Studies with pharmacological prevention of POST have used steroids, opioids, local anesthetics, nonsteroidal anti-inflammatory agents, alpha-2 agonists, and ketamine.<sup>5-13</sup>

Magnesium, an N-methyl-D-aspartate (NMDA) receptor antagonist, has potential advantages to play a beneficial role in reducing POST through multiple mechanisms, such as anti-nociceptive and anti-inflammatory effects by inhibiting NMDA receptor-mediated calcium influx.<sup>14</sup>

The previous studies have used magnesium sulfate for reducing POST in various routes such as intravenous (IV), nebulized form, and gargle.<sup>15-17</sup> There are no studies available comparing different routes of administration in prevention of POST. Hence, we undertook this study comparing IV route and nebulization of magnesium sulfate in the treatment of POST.

We selected percutaneous nephrolithotomy (PCNL) surgery patients as our subset as they are more prone for POST. Norm is to intubate with flexometallic tube with stylet and the procedure requires change in position from supine to prone and back from prone to supine leading to increased susceptibility to POST.

### Aims and objectives

Our primary objective was to determine which route of administration had lower incidence of POST. The secondary objectives in our study were to compare severity of POST between the two routes of administration along with hoarseness of voice between the nebulization and IV route.

## MATERIALS AND METHODS

This prospective randomized comparative double-blinded clinical trial was conducted after obtaining approval of Institutional Ethical Committee (IEC) and CTRI (CTRI/2020/09/028047) for 8 months in a tertiary care hospital from April 2021 to November 2021.

Adult patients between 18 and 65 years of age of either sex belonging to the American Society of Anesthesiology Status I and II, undergoing unilateral PCNL surgeries were included in the study. Exclusion criteria for this study were surgery involving the oral cavity, nasopharynx, larynx and neck regions, history of pre-operative sore throat, common cold, anticipated difficult airway, pregnant or lactating mothers, any recent use of anti-inflammatory drugs, and allergy to study drug. Pre-anesthetic evaluation was done for all the patients and written informed consent

was taken. Patients were explained regarding visual analog scale (VAS) score preoperatively and were randomized by an anesthesiologist not involved in patient care using computer-generated random numbers into two groups (Group N – Nebulized magnesium and Group I – IV magnesium) and group allocation was sealed in an opaque envelope.

On the day of surgery, all patients were secured with 18 G IV cannula and maintenance fluid started in pre-operative room and standard monitors were connected. The patient was blinded to study drug being administered. Both groups were given nebulization 20 min before induction by principle investigator and were monitored. Group N received 10 mg/kg magnesium sulfate in 5 mL of normal saline and Group I received 5 mL of normal saline through nebulization route.

In operation theater, standard monitors were attached and premedication with injection midazolam 0.02 mg/kg, glycopyrrolate 0.05 mg/kg, and fentanyl 1–2 mcg/kg was given 5 min before induction. After pre-oxygenation with 100% O<sub>2</sub> for 3 min, the patient was induced with injection propofol 2 mg/kg till the loss of verbal commands. Neuromuscular blockade to facilitate placement of endotracheal tube was achieved by injection vecuronium 0.1 mg/kg. Laryngoscopy was done with MacIntosh 3 or 4 blade and intubated with reinforced flexometallic tracheal tube of size 7 or 8 depending on gender of the patient with the help of rigid stylet. Normal saline was applied over the cuff for lubrication before intubation. The intubation was done by an experienced anesthesiologist not involved in the study. Cuff manometer was used to monitor intracuff pressure every 15 min and was kept between 20 and 25 cm of H<sub>2</sub>O.

Post-intubation, infusion of the study drug was given intravenously.

Group N received normal saline 100 mL over 20 min and Group I received 10 mg/kg of magnesium sulfate in 100 mL saline over 20 min through IV route.

Anesthesia was maintained with oxygen, nitrous oxide, isoflurane, and vecuronium. After the insertion of a urinary catheter, the patients were placed in the prone position for the surgery. A paravertebral block was performed in both the groups under ultrasound guidance with 23-gauge echogenic needle after identifying the landmarks at the T<sub>10</sub>-T<sub>11</sub> levels using 0.2% ropivacaine 25 mL after surgery in prone position. All blocks were performed by the same experienced anesthesiologist.

At the end of surgery, neuromuscular blockade was reversed with IV neostigmine 0.05 mg/kg and glycopyrrolate

0.01 mg/kg and suction was done with blunt tip catheter. Endotracheal tube was removed when the patient was completely awake.

The patients were shifted to the post-anesthesia care unit for further care after extubation. Postoperatively, VAS (0–10) was used for the assessment of severity of sore throat at rest and dynamic VAS (DyVAS) (0–10) was used for pain during swallowing, by an independent observer who was blinded to the study drugs. VAS score was assessed at the 0 h, 1<sup>st</sup> h, 6<sup>th</sup> h, 12<sup>th</sup> h, and 24<sup>th</sup> h along with vital parameters. Paracetamol 1 g IV with injection dexamethasone 8 mg was given when VAS or DyVAS was  $\geq 5$ , as a rescue analgesic up to 24 h.

Post-operative hoarseness was graded on 4-point score system at the 0 h, 1<sup>st</sup> h, 6<sup>th</sup> h, 12<sup>th</sup> h, and 24<sup>th</sup> h as: 0 – No complaint of hoarseness, 1 – Minimal hoarseness or change in quality of speech, 2 – Moderate hoarseness or change in quality of speech, and 3 – Severe change in quality of speech.<sup>18</sup>

Side effects of magnesium sulfate such as hypotension, diarrhea, and delayed recovery from anesthesia were recorded.

#### Sample size calculation and statistical analysis

Incidence of POST in the previous studies with IV magnesium sulfate was 37.5–50% and with nebulized magnesium sulfate was 19.2–30%.<sup>15,19-21</sup> Hence, sample size was estimated based on the previous study of Sheikh et al.,<sup>17</sup> where the incidence of POST was 48% with IV magnesium sulfate. Assuming a reduction of 50% in incidence with nebulized magnesium sulfate with alpha error 0.05 and power 80%, we acquired sample size of 68 per group. A total of 150 were taken to reduce the error due to loss of study subjects which is around 10%.

Data were entered into Microsoft Excel data sheet and were analyzed using SPSS 25 version (IBM SPSS Statistics, Somers NY, USA) software. Categorical data were represented in the form of frequencies and proportions and analyzed with Chi-square test. Qualitative data were represented with percentages and quantitative data were represented as mean with SD or median with interquartile range. Shapiro–Wilk test was applied to find normality. Mann–Whitney U-test was applied for comparison between medians.  $P < 0.05$  was considered as statistically significant.

## RESULTS

In our study, 150 study subjects were enrolled and randomized into two groups with 75 in each. In Group N, three patients were excluded due to traumatic intubation

and unanticipated difficult airway. In Group I, two patients were excluded due to traumatic intubation, and in three patients, study drug was stopped due to persistent hypotension (20% from pre-operative blood pressure (BP) for 5 min) on starting the drug infusion. The statistical analysis was done in remaining patients.

Mean age, gender, and duration of surgery were between Group I and Group N which were comparable and difference was not statistically significant as given in Table 1. Table 2 compares incidence of POST in Group I and Group N with an incidence of POST with IV magnesium being 52.86% compared to 29.17% in nebulized group with  $P = 0.004$  soon after extubation at 0 h which was statistically significant. Incidence was significantly lower in Group N at the 1<sup>st</sup> (29.17% vs. 52.86%) and 6<sup>th</sup> h (25% vs. 48.57%) compared to Group I.  $P = 0.004$  for both was statistically significant. There was no statistically significant difference in incidence between two groups at the 12<sup>th</sup> and 24<sup>th</sup> h.

Serial assessments of VAS at rest and DyVAS for POST with mean and median values are given in Table 3. As both the groups were administered magnesium sulfate as prophylaxis for POST, the VAS scores obtained were  $< 4$  and comparison was done with the help of both mean and median values. VAS scores were lower in Group N compared to Group I at the 0, 1<sup>st</sup>, and 6<sup>th</sup> h for both VAS at rest and DyVAS and  $P < 0.05$  was statistically significant. VAS at rest and DyVAS scores at the 12<sup>th</sup> and 24<sup>th</sup> h were similar between the two groups with  $p > 0.05$  is statistically not significant.

Median hoarseness was significantly lower in Group N receiving magnesium sulfate nebulization at the 0, 1<sup>st</sup>, and

**Table 1: Comparison of age and gender between two groups**

Variable	Group I (n=70)		Group N (n=72)		P-value
	Mean	SD	Mean	SD	
Age	36.67	13.10	38.25	10.39	0.289
Gender (M/F)	32/38		27/45		0.32
Duration of surgery	174 $\pm$ 35 min		183 $\pm$ 37 min		0.138

**Table 2: Comparison of incidence of POST in two groups at each time interval**

Incidence	Group I (n=70)		Group N (n=72)		P-value
	Count	%	Count	%	
0 h	37	52.86	21	29.17	<b>0.004</b>
1 <sup>st</sup> h	37	52.86	21	29.17	<b>0.004</b>
6 <sup>th</sup> h	34	48.57	18	25.00	<b>0.004</b>
12 <sup>th</sup> h	20	28.57	16	22.22	0.38
24 <sup>th</sup> h	9	12.86	12	16.67	0.52

POST: Post-operative sore throat

6<sup>th</sup> h with P=0.004, <0.001, and <0.001, respectively, which were statistically significant. At the 12<sup>th</sup> h and 24<sup>th</sup> h, there was no significant difference between the two groups (Table 4).

At all intervals, there was no significant difference in mean heart rate and mean systolic BP, diastolic BP, and MAP values between the two groups. The mean SpO<sub>2</sub> and respiratory rates were comparable between two groups. In Group I, three patients were excluded from the study as the study drug infusion was stopped and due to persistent hypotension.

## DISCUSSION

Magnesium is present in our body as the fourth most common cation, predominantly found in the intracellular compartment and has been an ion under scrutiny for a long time. It regulates calcium influx into cell and brings about its actions through NMDA receptor antagonism.<sup>22</sup> Studies have shown change in intracellular calcium levels lead to excitability of the neurons and have a role in perception of pain.<sup>23</sup> Hence, MgSO<sub>4</sub> regulates calcium influx into the cell and has anti-nociceptive action.

We conducted this randomized comparative double-blinded study to determine the superior route of administration between IV and nebulized magnesium sulfate. Many routes of administration have been used for MgSO<sub>4</sub> such as IV, nebulization, gargle, and lozenges.<sup>15-19</sup>

The incidence of POST was less with group nebulized with magnesium, that is, Group N (29% at 0 h) compared to Group I where magnesium was administered intravenously (52.86% at 0 h). The incidence at the 1<sup>st</sup> h (29.17% vs. 52.86%) and at the 6<sup>th</sup> h (25% vs. 48.57%) also showed lesser POST in Group N nebulized with magnesium sulfate. The difference in incidence was statistically significant at the 0, 1<sup>st</sup>, and 6<sup>th</sup> h (Table 2). In a study conducted by Park et al., and Sheik et al., the overall incidence of POST with IV magnesium sulfate was 58.9% and 48%, respectively.<sup>15,17</sup> In their study, Park et al., administered 30 mg/kg bolus of magnesium sulfate with 10 mg/kg infusion intravenously and Sheik et al., had given 30 mg/kg magnesium sulfate infusion. Studies conducted by Jain et al., and Kamel et al., where nebulized form of magnesium was used, incidence of POST was 30% and 19.2%, respectively.<sup>20,21</sup> Jain et al., had administered 225 mg of magnesium sulfate in nebulized form and Kamel et al., had given 250 mg of nebulized magnesium. The incidences of POST in the above studies are similar to the results obtained in our study. IV route of administration can assure 100% bioavailability of the drug compared to nebulized routes which are considered inefficient with large amount of drug wastage (>50%).<sup>24</sup> However, studies have shown lesser incidence of POST with nebulized route. This may be due to better local action on the mucosa of pharynx. Park et al., in their study, administered 30 mg/kg bolus of magnesium sulfate with 10 mg/kg infusion intravenously and 72.6% of the participants had at least one episode of hypotension.<sup>15</sup>

**Table 3: Comparison of VAS at rest and dynamic VAS between two groups**

Variable	Type of VAS	Group I				Group N				P-value
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	
VAS at 0 h	At rest	1.24	1.23	2.00	2.00	0.76	1.20	0.00	2.00	<b>0.022</b>
	Dynamic	1.60	1.60	2.00	3.00	0.97	1.57	0.00	3.00	<b>0.022</b>
VAS at 1 <sup>st</sup> h	At rest	1.10	1.11	1.00	2.00	0.58	0.96	0.00	1.75	<b>0.004</b>
	Dynamic	1.33	1.36	2.00	2.25	0.82	1.35	0.00	2.00	<b>0.024</b>
VAS at 6 <sup>th</sup> h	At rest	0.74	0.86	0.00	1.25	0.42	0.76	0.00	0.75	<b>0.009</b>
	Dynamic	0.90	0.99	1.00	2.00	0.64	1.12	0.00	1.75	<b>0.032</b>
VAS at 12 <sup>th</sup> h	At rest	0.34	0.59	0.00	1.00	0.31	0.62	0.00	0.00	0.478
	Dynamic	0.31	0.71	0.00	0.00	0.32	0.65	0.00	0.00	0.775
VAS at 24 <sup>th</sup> h	At rest	0.14	0.39	0.00	0.00	0.19	0.43	0.00	0.00	0.402
	Dynamic	0.20	0.47	0.00	0.00	0.26	0.58	0.00	0.00	0.653

VAS: Visual analog scale, IQR: Interquartile range

**Table 4: Comparison hoarseness of voice between Group I and Group N**

Variable	Group I				Group N				P-value
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	
HV at 0	0.80	0.84	1.00	2.00	0.40	0.64	0.00	1.00	<b>0.004</b>
HV at 1	0.54	0.56	1.00	1.00	0.24	0.43	0.00	0.00	<b>&lt;0.001</b>
HV at 6	0.37	0.49	0.00	1.00	0.11	0.32	0.00	0.00	<b>&lt;0.001</b>
HV at 12	0.04	0.20	0.00	0.00	0.00	0.00	0.00	0.00	0.077
HV at 24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.000

IQR: Interquartile range, SD: Standard deviation



This was treated with administering fluids, incremental doses of ephedrine, and if hypotension still persisted with phenylephrine or noradrenaline infusion. We wanted to avoid this side effect hence chose dose of 10 mg/kg of magnesium sulfate in both groups and found that reduction in incidence of POST with lower doses was similar to higher doses.

In our study, VAS at rest and DyVAS were checked to assess severity of POST at the 0, 1<sup>st</sup>, 6<sup>th</sup>, 12<sup>th</sup>, and 24<sup>th</sup> h. As both the groups received prophylaxis in the form of magnesium sulfate to prevent POST, the VAS scores were below 4 at all times (Table 3). Hence, rescue analgesia was not used in both groups. However, the scores were lower in the Group N nebulized with magnesium at the 0, 1<sup>st</sup>, and 6<sup>th</sup> h and differences in scores were statistically significant. The VAS scores both at rest and on swallowing were less in Group N. This might be because of better local action through nebulized route.

We observed in our study that the hoarseness of voice was significantly lower in Group N at the 0, 1<sup>st</sup>, and 6<sup>th</sup> h compared to Group I with  $P=0.004$ ,  $<0.001$ , and  $<0.001$ , respectively. There was no significant difference between two groups with respect to hoarseness score at the 12<sup>th</sup> and 24<sup>th</sup> h (Table 4).

Three study subjects had persistent hypotension with initiation of IV MgSO<sub>4</sub> infusion and were excluded from the study as full study drug could not be administered. The mean heart rate and mean blood pressures in the remaining subjects in both the groups were within normal limits and were comparable with no significant difference. There were no other side effects of MgSO<sub>4</sub> seen such as delayed recovery from anesthetics, bradycardia, or diarrhea.

Nebulized route is easy to administer, no side effects like hypotension seen in IV routes, provide better pain relief compared to IV route, and can be a preferred modality for the prevention of POST.

#### Limitations of the study

We have excluded patients with difficult airway in our study. We could not include the patients with hypotension after administration of IV MgSO<sub>4</sub> as study drug was discontinued.

## CONCLUSION

Incidence of POST was lower with nebulized magnesium sulfate compared with IV magnesium sulfate. Nebulization can be preferred route of drug administration for the prevention of POST.

## FUTURE SCOPE

Further studies are required for wide spread use of nebulized magnesium sulfate in different doses and with different routes.

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**R-** concept and design of study, literature review, interpretation of results, and preparation of manuscript. **SK-** Data collection, statistical analysis and interpretation, and preparation of manuscript. **SMJI-** concept and design of the study, interpretation of results, and revision of manuscript.

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