

## A COMPARATIVE STUDY BETWEEN PREEMPTIVE MAGNESIUM SULPHATE AND GABAPENTIN IN THE MANAGEMENT OF POSTOPERATIVE PAIN IN ADULTS.

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### ABSTRACT.

#### Introduction:

Control of perioperative pain is an important aspect of anesthesia. Though several methods have been tried, pre-emptive analgesia is a debatable concept. Magnesium, an NMDA antagonist, and gabapentin, an alpha2 delta subunit of the calcium channel blocker were used as adjuvants to control perioperative pain. The objective of the present study was to compare the postoperative analgesic effect of Oral Gabapentin 10mg/kg with IV Magnesium Sulphate 50mg/kg in patients undergoing surgery under Regional Anaesthesia.

#### Materials and methods:

Sixty patients were divided into two groups where group A received 10mg/kg of gabapentin and group B received 50mg/kg of magnesium sulphate before spinal anesthesia. Intraoperative HR, NIBP, ECG, SPO2, urine output, and deep tendon reflexes were monitored. The sedation status of patients was assessed by the Ramsay Sedation Score. The degree of pain in the Postoperative period was assessed by VAS score at intervals of 4hrs up to the first 24hrs and with a VAS score of more than 3, Inj Diclofenac 75mg was given intramuscularly as the rescue analgesic.

#### Observation:

The patients in the gabapentin group achieved sensory and motor block in 6.2 and 6.3 minutes respectively while patients in the magnesium sulphate group took longer time for the same i.e. 8.1 and 8.4 minutes respectively which was statistically significant (p-value < 0.001). The pain score was significantly lower in the gabapentin group compared to the magnesium group (p-value < 0.05). The requirement for rescue analgesia was higher in the magnesium sulfate group but was not statistically significant.

#### Conclusion:

Pain score was significantly lower among the patients in the gabapentin group compared to the magnesium sulfate group at different time intervals. Hypotension was observed in a few patients in the magnesium sulfate group.

#### Recommendation:

Magnesium sulfate as pre-emptive analgesia should be considered to reduce the postoperative requirement of analgesics.

**Keywords:** Pre-emptive analgesia, Magnesium sulfate, Gabapentine, Post-operative analgesia

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### INTRODUCTION.

Traditionally, acute perioperative pain management is addressed by opioid medications. Now worldwide multimodal therapy to pain is the optimal choice for perioperative pain control to minimize the side effects of a large dose of opioids<sup>1</sup>. The perioperative pain is initiated either by an inflammatory process induced by tissue

trauma or by direct nerve injury. Tissue trauma initiates pain through local inflammatory mediators that augment the sensitivity to stimuli (hyperalgesia) or even misperception of pain (allodynia). Hyperalgesia and allodynia are also caused by sensitization of the peripheral pain receptors, primary hyperalgesia, and increased excitability of central nervous system neurons, secondary hyperalgesia<sup>2,3,4</sup>. The concept of "pre-emptive" analgesia

means that analgesic strategies are administered before surgical incision or stimulus to modify the peripheral and central nervous system to noxious stimuli, thereby reducing central sensitization, hyperalgesia, and allodynia<sup>2,3,4</sup>. Several studies have concluded that preoperative timing is not necessary to achieve a reduction in postoperative pain and opioid use<sup>5</sup>.

Magnesium is a non-competitive *N*-methyl D-aspartate (NMDA) receptor antagonist with analgesic effects<sup>6</sup>. Perioperative magnesium sulfate reduces the need for anesthetics and improves postoperative analgesia<sup>7</sup>. However, magnesium ion poorly crosses the blood-brain barrier in humans, not clear whether the therapeutic effect is related to NMDA antagonism in the central nervous system, dorsal horn NMDA receptors, or peripheral action<sup>8</sup>. Owing to the “protective” effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery<sup>5</sup>. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented<sup>3</sup>. Gabapentin was initially introduced as an antiepileptic drug for partial seizure and is beneficial in treating neuropathic pain related to post-herpetic neuralgia, post-poliomyelitis neuropathy, reflex sympathetic dystrophy, and diabetic neuropathy. Gabapentin works by reducing hyperexcitability of posterior horn neurons which are responsible for central sensitization<sup>9</sup>. The mechanism of the analgesic action may be the result of the postsynaptic binding of gabapentin to the alpha2- delta subunit of the dorsal horn neurons' voltage-dependent calcium channels causing decreased calcium entry into nerve endings and thus decreasing the release of neurotransmitters. Other possible cellular mechanisms include the effects of gabapentin on NMDA receptors, sodium channels, monoaminergic pathways, and the opioid system<sup>10</sup>. Oguzhan *et al.*<sup>11</sup> (2008) results suggested that intraoperative magnesium administration significantly reduced intraoperative muscle relaxant and opioid requirements and reduced postoperative pain and opioid use. When used during a variety of surgeries, magnesium was also found to reduce the need for intraoperative anesthetics and muscle relaxants and to reduce the amount of morphine required to treat postoperative pain. Ryu *et al.*<sup>12</sup> (2009) compared remifentanyl and magnesium during middle ear surgery and found that magnesium or remifentanyl combined with sevoflurane provided adequate hypotensive anesthesia but patients in the magnesium group experienced a more comfortable

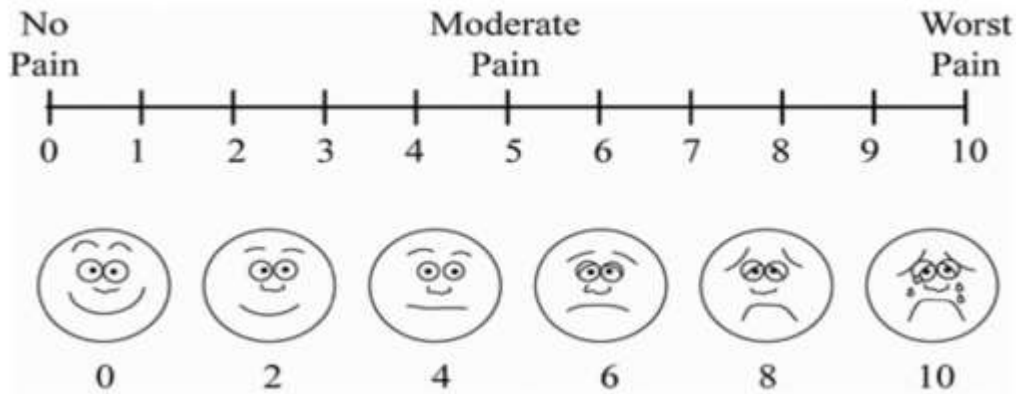
postoperative course with better analgesia, less shivering and less postoperative nausea and vomiting (PONV). Ucak *et al.*<sup>13</sup> evaluated the analgesic effects of perioperative gabapentin after coronary artery bypass graft (CABG) surgery with median sternotomy as well as internal mammary artery harvesting and used a gabapentin dose of 1.2 g per day treatment 1 hour before surgery and for 2 days after surgery. In this study, postoperative pain scores at 1, 2, and 3 days as well as the consumption of tramadol which was given as rescue analgesic were significantly lower in the gabapentin group when compared to the placebo group. So the current study was planned to find out the efficacy of pre-emptive magnesium sulfate compared to gabapentin in terms of analgesia in post-operative pain management.

### **Aim of the study.**

The objective of the present study was to compare the postoperative analgesic effect of Gabapentin 10mg/kg and IV Magnesium Sulphate 50mg/kg in patients undergoing surgery under regional anesthesia.

### **Materials and Methods.**

This was an institution-based double-blinded comparative study carried out in a medical institution MKCG Medical College and Hospital Berhampur, in the eastern part of India from June 2021 to December 2022, in sixty patients of ASA I and II, of either sex in the age group of 18 to 60 years. Patients with contraindications to epidural anesthesia, allergy to local anesthetics, cardiac or psychiatric disease, coagulation disorders, hemodynamic instability, or history of drug abuse were excluded from the study. Patients were sequentially enrolled into Group A and Group B according to a predefined scheme, in which the first participant was allocated to Group A and the next participant to Group B followed by a reversal of the group allocation. This process continued till thirty participants in each group were obtained. Group A received Gabapentine 10mg/kg. Group B received Magnesium Sulphate 50mg/kg. After a thorough pre-anesthetic check-up, consent was obtained from all patients. Patients were explained about the visual analog scale/ VAS scale which is a 10-point scale indicating 1- no pain and 10- severe excruciating pain.



### Visual analog scale

The patients were kept fasting for 6 hours before the surgery. The baseline heart rate (HR), non-invasive blood pressure (NIBP), electrocardiogram (ECG), oxygen saturation (SpO<sub>2</sub>), and sedation status of the patients were recorded. Patients belonging to Group A received Gabapentin in a dose of 10mg/kg 2hrs before surgery in 100ml of isotonic Sodium Chloride solution IV and Group B received Magnesium Sulfate in a dose of 50mg/kg in 100ml of isotonic Sodium Chloride solution just before surgery. Spinal anesthesia was given using Bupivacaine in all patients and surgery was allowed after ascertaining adequate blockade. As this was a double-blinded study both the patients and drug administrators were blinded about the study drugs. Intraoperative HR, NIBP, ECG, Oxygen saturation, Urine Output, and Deep Tendon reflexes were monitored. The sedation status of patients was assessed by the Ramsay Sedation Score as follows: -

- Anxious, agitated restless, or both.
- Cooperative, oriented & tranquil.
- Responds to verbal commands.
- Exhibits brisk response to light tactile stimuli or loud auditory stimuli.
- Exhibits sluggish response to light tactile stimuli or loud auditory stimuli.
- Exhibits no response.
- Perioperative fall in HR & BP of more than 30% from the baseline value was treated with atropine (0.6mg) and IV fluids and incremental doses of ephedrine 5mg respectively. Fall in SpO<sub>2</sub> below 95% was treated with oxygen inhalation by facemask.

The degree of pain in the Postoperative period was assessed by VAS score at intervals of 4hrs up to the first

24hrs along with HR, NIBP, and Oxygen saturation, and with a VAS score of more than 3, Inj Diclofenac 75mg was given intramuscularly as the rescue analgesic.

- The following parameters were recorded
- Name, age, sex, height, weight, ASA grades
- Type of surgery
- Time of commencement of surgery
- Total period of surgery
- Time for the need for 1st rescue analgesia
- The total dose of rescue analgesia needed in the first 24hrs
- Perioperative hemodynamic parameters and O<sub>2</sub> saturation.
- Side effects like nausea, vomiting, respiratory depression, drowsiness, etc

### Statistical analysis.

The collected data were entered into Microsoft Excel (MS-EXCEL, Microsoft Corp.) data sheet and analyzed with the statistical program Statistical Package for the Social Sciences (IBM SPSS, version 17). Data were organized and presented using the principles of descriptive and inferential statistics. The data were categorized and expressed in proportions. The continuous data were expressed as mean±SD.

1. Student t-test and Mann-Whitney U test for parametric data.
  2. Chi-square test for non-parametric data.
- P<0.05 was considered statistically significant.

### OBSERVATION.

**Table 1: Comparison of baseline characteristics of the study participants.**

Characteristics	Gabapentin Group N (%)	MgSO <sub>4</sub> Group N (%)	P value
Gender			
Male	18 (60.0)	14 (46.7)	0.301
Female	12 (40.0)	16 (53.3)	
Age group			
< 40 years	15 (50.0)	16 (53.3)	0.796
≥ 40 years	15 (50.0)	14 (46.7)	
ASA group			
I	25 (83.3)	28 (93.3)	0.228
II	5 (16.7)	2 (6.7)	

Weight	63.80 ± 13.20	65.50 ± 15.90	0.654
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The mean age of the study participants was 42.53 ± 4.5 years in the gabapentin group while the mean age was 43.56 ± 3.6 years in the magnesium sulfate group. Age group-wise distribution suggested that participants were equally distributed in both less than 40 years and 40 years or above age brackets with a p-value of 0.796. Gender-wise distribution suggested that a slightly higher proportion of males in the gabapentin group (60%) compared to the magnesium sulphate group (46.7%). This

difference in proportion was also not statistically significant (P-value = 0.301). Similarly, we did not find any statistically significant difference concerning the ASA category between the groups. The mean weight of the patients in the gabapentin group was 63.80 ± 13.20 kgs while it was 65.50 ± 15.90 kgs in the magnesium sulfate group and was not statistically significant. The two groups were comparable concerning the baseline characteristics.

**Table 2: Comparison of intraoperative parameters between the groups.**

Parameters	Gabapentin Group		Magnesium sulfate Group		P value
	Mean	SD	Mean	SD	
Duration of surgery (mins)	100.60	10.77	98.70	10.96	0.501
Sensory block (mins)	6.20	1.29	8.10	2.41	<0.001
Motor block (mins)	6.30	0.79	8.47	2.06	<0.001
Time to analgesia (mins)	45.40	8.68	44.53	7.92	0.688

The mean duration of surgery was comparable in the gabapentin group (100 mins) compared to the magnesium sulfate group (98 mins) with a p-value of 0.501 (Table 2). The patients in the gabapentin group achieved sensory and motor block in 6.2 and 6.3 mins respectively while

patients in the magnesium sulfate group took longer time for the same i.e. 8.1 and 8.4 mins respectively. This difference was statistically significant (p-value < 0.001). Time to analgesia was comparable in both groups.

**Table 3: Comparison of VAS scores at different time intervals across the groups.**

VAS score	Gabapentin Group		Magnesium sulfate group		P-value
	Mean	SD	Mean	SD	
Baseline	5.33	1.061	5.9	1.242	0.062
1 hr	4.97	1.159	6.07	1.202	0.001
2 hrs	4.03	1.129	5.23	1.278	<0.001
4 hrs	4.47	1.008	5.63	1.189	<0.001
8 hrs	4.37	1.033	5.53	1.137	<0.001
12 hrs	4.47	0.937	5.43	1.135	0.001
16 hrs	4.2	0.887	5.4	1.102	<0.001
20 hrs	4.3	0.877	5.3	1.179	<0.001
24 hrs	2.87	0.973	3.9	1.322	0.001

The primary objective of the study was to compare the pain reduction in both interventions and the details are given in Table 9 and Figure 14. Except just after the

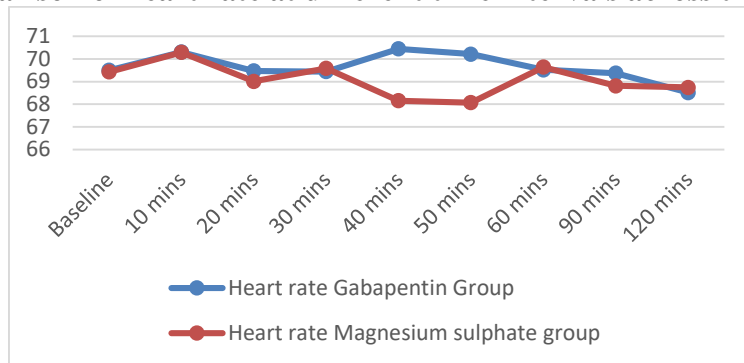
surgery, the pain score was significantly lower in the gabapentin group compared to the magnesium sulfate group (p-value < 0.05).

**Table 4: Comparison of Ramsay sedation score of the study participants between the groups.**

	Gabapentin Group (Mean ± SD)	MgSO <sub>4</sub> Group (Mean ± SD)	P value
Ramsay Sedation score	4.83 ± 0.791	4.87 ± 0.819	0.873

The Ramsay sedation score was comparable in both groups.

**Figure 1: Comparison of heart rate at different time intervals across the groups**



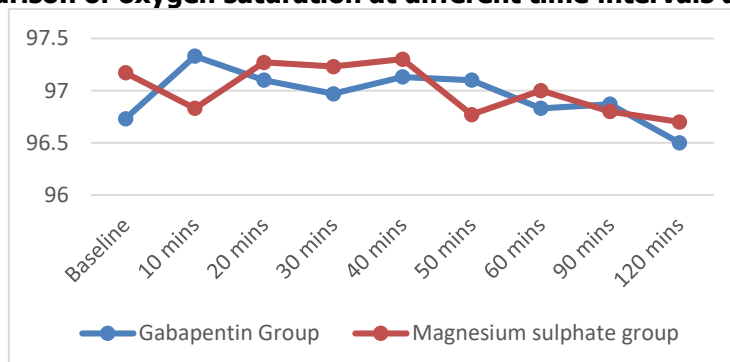
There was no significant difference in heart rate at different time intervals except for at 40 and 50 mins where heart rate was higher in the gabapentin group compared to the magnesium sulphate group and this difference was statistically significant.

**Table 5: Comparison of mean arterial pressure at different time intervals.**

MAP	Gabapentin Group		Magnesium sulfate group		P value
	Mean	SD	Mean	SD	
Baseline	100.13	2.54	99.13	2.46	0.657
10 mins	98.30	4.12	95.86	3.88	<0.001
20 mins	97.33	4.06	94.41	4.15	<0.001
30 mins	97.02	3.85	94.09	3.64	<0.001
40 mins	98.17	3.93	94.86	4.01	<0.001
50 mins	97.97	4.36	95.69	3.35	0.034
60 mins	96.62	4.04	95.64	3.25	0.546
90 mins	96.38	3.76	96.76	4.04	0.657
120 mins	95.12	3.88	95.47	3.76	0.765

The gabapentin group had higher mean arterial pressure at 10 minutes, 20 minutes, 30 minutes, 40 minutes, and 50 minutes compared to the magnesium sulfate group and this difference was statistically significant.

**Figure 2: Comparison of oxygen saturation at different time intervals across the groups.**



We did not find any statistically significant difference in Oxygen saturation at different time intervals between the groups.

**Table 6: Comparison of side-effects and requirement rescue analgesia between the groups.**

Characteristics	Gabapentin Group N (%)	MgSO <sub>4</sub> Group N (%)	P value
Number of rescue analgesia			
0	24 (80.0)	17 (56.7)	0.149
1	4 (13.3)	8 (26.7)	
2	2 (6.7)	5 (16.7)	
Side effects			
None	27 (90.0)	25 (83.3)	0.354
PONV	3 (10.0)	3 (10.0)	
Hypotension	0 (0)	2 (6.7)	

Although the requirement for rescue analgesia was higher in the magnesium sulphate group the difference was not statistically significant. Hypotension was only observed as a side-effect in the magnesium sulphate group while it was found that a similar proportion of subjects had post-operative nausea and vomiting in both groups.

## DISCUSSION.

The objective of the study was to compare the efficacy of gabapentin and pre-emptive magnesium sulphate in the reduction of post-operative pain. In the current study, it was found that the mean age of the study participants was  $42.53 \pm 4.5$  years in the gabapentin group while the mean age was  $43.56 \pm 3.6$  years in the magnesium sulphate group. The participants were equally distributed in both groups with p value of 0.796. Gender-wise distribution suggested that a slightly higher proportion of males in the gabapentin group (60%) compared to the magnesium sulphate group (46.7%). This difference in proportion was also not statistically significant (P-value = 0.301). Similarly, we did not find any statistically significant difference concerning the ASA category between the groups. The mean weight of the patients in the gabapentin group was  $63.80 \pm 13.20$  kgs while it was  $65.50 \pm 15.90$  kgs in the magnesium sulphate group and was not statistically significant (P value = 0.654) This means the patients in both groups were comparable concerning baseline characteristics.

The mean duration of surgery was 100 minutes in the gabapentin group compared to the magnesium sulphate group 98 minutes with a p-value of 0.501. The patients in the gabapentin group achieved sensory and motor block in 6.2 and 6.3 minutes respectively while patients in the magnesium sulphate group took longer time for the same i.e. 8.1 and 8.4 mins respectively. This difference was statistically significant (p-value < 0.001). Time to analgesia was comparable in both groups (Table 2).

Figure 1 showed no difference in heart rate at different time intervals except for at 40 and 50 mins where heart rate was higher in the gabapentin group compared to the magnesium sulfate group and this difference was statistically significant. Patients in the gabapentin group had higher mean arterial pressure at 10 minutes, 20 minutes, 30 minutes, 40 minutes, and 50 minutes compared to the magnesium sulphate group and this difference was statistically significant. (Table 5)

Table 3 showed except just after the surgery, the pain score was significantly lower in the gabapentin group compared to the magnesium sulphate group (p-value < 0.05). Although the requirement for rescue analgesia was higher in the magnesium sulphate group the difference was not statistically significant. Hypotension was only observed as a side-effect in the magnesium sulfate group while it was found a similar proportion of subjects had postoperative nausea and vomiting in both groups.

Tramer et al.<sup>14</sup> conducted the first prospective, randomized study on the effect of magnesium on analgesic requirements and showed that magnesium sulphate reduced analgesic requirements and discomfort and improved the quality of sleep during the postoperative period without any adverse effects at 48 hrs after surgery. Oguzhan et al.<sup>11</sup> (2008) studied the effect of a magnesium sulphate infusion on postoperative requirements for opioids, intraoperative muscle relaxants, and post-operative pain during and after lumbar disc surgery and their results suggested that intraoperative magnesium administration significantly reduced intraoperative muscle relaxants and opioid requirements and also reduced postoperative pain and opioid use.

Ryu et al.<sup>12</sup> (2009) compared remifentanyl and magnesium during middle ear surgery and found that magnesium or remifentanyl combined with sevoflurane provided adequate hypotensive anesthesia, but patients in the magnesium group experienced a more comfortable postoperative course with better analgesia, less shivering and less postoperative nausea and vomiting. Furthermore, the amount of sevoflurane required to maintain surgical anesthesia was significantly lower in the magnesium group than in the remifentanyl group.

Magnesium was found to prevent the induction of central sensitization by peripheral nociceptive stimulation at a spinal site of action by blocking NMDA receptors in a voltage-dependent fashion<sup>15</sup>. Utilizing the same mechanism, the addition of small doses of magnesium sulfate to local anesthetics for spinal anesthesia enhanced the duration of anesthesia and reduced postoperative analgesic requirements and the incidence of side effects of high doses of local anesthetics and opioids.

However, not all investigations have reported postoperative analgesic effects for magnesium sulfate. Perioperative magnesium infusion was not found to reduce postoperative pain or analgesic consumption in patients undergoing abdominal hysterectomy<sup>16</sup> or cesarean delivery<sup>17</sup>. Furthermore, in a recent report by

Tramer and Glynn<sup>18</sup> (2007), pretreatment with magnesium sulfate was found to have no effect on postoperative pain or analgesic requirements over the first three postoperative days in patients undergoing ambulatory ilioinguinal hernia repair or varicose vein surgery. However, in this study, a single dose (4 g) of intravenous magnesium sulfate was used instead of a loading dose plus continuous infusion.

Magnesium acts as a calcium channel blocker at presynaptic nerve terminals and reduces acetylcholine release at the motor endplate<sup>19</sup>. This diminishes muscle fiber excitability and reduces end plate potential amplitudes which leads to the potentiation of a neuromuscular blockade by nondepolarizing neuromuscular blockers.

Zakkar et al.<sup>23</sup> in a meta-analysis found the use of gabapentin to reduce the incidence of pain experienced by patients after thoracic surgery and concluded that there is no evidence to support the role of a single preoperative oral dose of gabapentin in reducing pain scores or opioid consumption after thoracic surgery. Furthermore, more robust randomized control studies were needed to validate the efficacy of multiple dosing regimens but studies currently showed that it might be beneficial in reducing acute pain. Lee et al.<sup>20</sup> explored the efficacy of using gabapentin (600 mg) 1 hour before the administration of anesthesia for thyroid surgery and had a lower incidence of postoperative sore throat (POST) and a significantly lower visual analog scale (VAS) score of 6 and 24 hours after the completion of the surgery compared to the placebo group. However, there was no intergroup difference between the gabapentin group and the placebo group in terms of the incidence of POST or VAS score during the swallowing movement.

Misra et al.<sup>21</sup> performed a study to investigate patients undergoing craniotomies and the efficacy of gabapentin plus dexamethasone on postoperative nausea and vomiting (PONV) and pain after craniotomy. Patients undergoing craniotomy received gabapentin (600 mg) premedication orally 2 hours before induction of anesthesia as well as 4 mg of intravenous dexamethasone on the morning of surgery and continued receiving it every 8 hours. This study observed a significant difference between gabapentin, dexamethasone, and the placebo group in the incidence of nausea and the requirements for antiemetics. However, there was no significant difference in either the postoperative pain scores or the opioid consumption between the gabapentin with dexamethasone cohort and the placebo cohort.

Yu et al.<sup>22</sup> performed a systematic review and meta-analysis to determine the efficacy of gabapentin in the management of postoperative pain after lumbar spine surgery. They showed that oral gabapentin was efficacious in the management of postoperative pain at every time point during the first day after surgery and therefore was efficacious in reducing postoperative pain and narcotic requirements after lumbar spinal surgery.

## CONCLUSION.

Since the baseline characteristics were comparable in both the groups in our study the effect on the pain reduction was most likely due to the intervention i.e., gabapentin and pre-emptive magnesium sulphate. Pain score was significantly lower among the patients in the gabapentin group compared to the magnesium sulphate group at different time intervals. Lower systolic, and diastolic blood pressure and mean arterial pressure were observed in the magnesium sulphate group compared to the gabapentin group. Hypotension was observed in a few patients in the magnesium sulphate group. Side effects like postoperative nausea and vomiting were comparable in both gabapentin and magnesium sulphate groups.

## LIMITATIONS OF THE STUDY.

A small sample size may compromise the generalizability of the study. So we recommend a large randomized controlled trial to confirm this evidence.

## GENERALIZABILITY.

This study is generalizable to other studies of a similar kind.

## ACKNOWLEDGMENT.

We are very much indebted to the faculties of anaesthesiology for their cooperation and the patients for their participation and patience.

## ABBREVIATIONS.

HR-	Heart Rate
NIBP-	Non-invasive blood pressure
ECG-	Electrocardiogram
SPO2-	Oxygen Saturation
PONV-	Post-operative Nausea and Vomiting
VAS-	Visual Analogue scale
CABG-	Coronary arteries bypass graft

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There is no funding of any kind from the external agencies.

## CONFLICT OF INTEREST.

There is no conflict of interest between the authors.

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