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ORIGINAL ARTICLE

A STUDY ON PERI-OPERATIVE MAGNESIUM SULPHATE ON POST-OPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING PELVIC AND LOWER LIMB SURGERIES

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ABSTRACT: CONTEXT: Post-operative pain is the major morbidity of most of the surgeries. This study aims to find out the analgesic property of MAGNESIUM SULPHATE as it blocks N-Methyl D-Aspartate receptor. **AIMS:** To study the effect of Peri-operative IV Magnesium sulphate on Post-operative pain management and to determine the adverse reactions, if any. **SETTINGS AND DESIGN:** This prospective study is double-blind, randomised, placebo controlled clinical trial among the patients undergoing elective lower limb and pelvic surgery under spinal anaesthesia. **METHODS AND MATERIAL:** 60 ASA 1 & 2 patients aged between 18 and 50 years was selected and assigned to two groups 'M' group for magnesium and 'S' group for placebo. 'M' group was infused with 500ml normal saline containing Inj. Magnesium sulphate at a dose of 8mg/kg body weight/hour till the end of the surgery. The placebo group 'S' also received same amount of normal saline till the end. Post-operative pain analysis was done with VAS scoring system at 3, 6, 12 & 24 hours. **STATISTICAL ANALYSIS USED:** Data analysis was done with SPSS software. To present the results, mean+SD was used and a 'P' value of < 0.05 was considered statistically significant. **RESULTS:** There existed a statistically significant difference in mean VAS within the groups during the observation period (p-value <0.000). The highest mean VAS in M groups was recorded at 12 hours and in S group at 6 hours. Only 22 patient required morphine for pain relief in M group while all patients in group S required morphine. The total dose of morphine used was higher in the placebo group. But this mean difference was not statistically significant (p-value = 0.43). The total dose of magnesium used and the post-operative morphine requirement showed a strong inverse relation with a p-value of < 0.0001. The rescue analgesic requirement was delayed in M group (p-value of 0.01) **CONCLUSIONS:** We hypothesis that peri-operative IV Magnesium prolongs the first analgesic requirement with a reduction in total pain scores and the analgesic requirement without any increase in adverse reactions. This signifies the role of magnesium in multimodal preventive analgesia.

KEYWORDS: Post-operative pain, magnesium sulphate, spinal anaesthesia, peri-operative.

KEYMESSAGES: Magnesium will be promising adjuvant to multi-model analgesia especially for complete preventive analgesia.

INTRODUCTION: International Association for the Study of Pain defines Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] Pain serves a biological function. It signals the presence of damage or disease within the body. In case of postoperative pain; it is the result of the surgery. Thus it is considered as "the fifth vital sign" by the Joint Commission on Accreditation of Healthcare Organisation. Effective in 2001, the JCAHO requires adequate assessment, monitoring, and treatment

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of pain as one of the condition for accreditation.[2] Pain management must become part of all patient care activities.

Most important concern of patients before surgery is regarding the post-operative pain. Because of its close ties with clinical outcome and post-operative patient well-being, post-operative pain is also a major concern for surgeons. In a national survey conducted in US, suggests that post-operative pain continues to be under-managed.[3] The goal for postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects as cheaply as possible. Postoperative pain relief must reflect the needs of each patient. The ultimate determinant of the adequacy of pain relief will be the patient's own perception of pain.[4] As said by the father of pain medicine, Dr John Bonica: “Pain is what a patient says it is”.

Undermanaged postoperative pain may result in clinical and psychological changes that increase morbidity and mortality as well as costs and that decrease quality of life.[5] Ineffective postoperative pain management can lead to decrease in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia and infarction, deep vein thrombosis, pulmonary embolism, transition to chronic pain syndrome, poor wound healing, insomnia and psychological distress[5-6]. Associated with these complications are economic and medical implications, such as extended lengths of stay, readmissions, and patient dissatisfaction with medical care.[7-8]

Now the preferred mode of post-operative analgesia is the ‘Balanced(Multimodal) Analgesia’; uses two or more analgesic agents that act by different mechanisms to achieve a superior analgesic effect without increasing adverse events compared with increased doses of single agents. For example, epidural opioids can be administered in combination with epidural local anaesthetics; intravenous opioids can be administered in combination with NSAIDs, which have a dose sparing effect for systemically administered opioids. Balanced analgesia is therefore the method of choice wherever possible.[9]

Since the major surgical morbidity is due to post-operative pain, effective control of it will drastically improve the total surgical outcome i.e. improves pulmonary function by preventing pain induced diaphragmatic splinting and thereby hypoventilation,[4] more rapid return of gastric emptying, earlier bowel movements and lesser nausea and vomiting.[10] It helps in achieving better hemodynamic status, early ambulation and reduces surgical stress response.

For post-operative pain control, commonly used drug is opioid especially Morphine. PCA-Patient Controlled Analgesia is an established way of drug delivery system. Presently drug delivering pumps are used which deliver specified amount of drug at a constant rate. For the effective pain control, the amount of opioid consumption is found to be large enough to cause potential respiratory and hemodynamic suppression and higher incidence of nausea and vomiting.[11]

Magnesium, which is the fourth most prevalent cation in the body; second most prevalent intracellular cation; blocks the NMDA receptor at normal state, so that neither Acetyl Choline can cross the synaptic cleft nor glutamate can activate the NMDA receptor. Due to this action it has been studied for management in pain, especially as adjuvant for balanced analgesia.

The first clinical study showed that the perioperative application of magnesium sulphate is associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period without any adverse effects was done by Tramer Martin et al.[12]

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Intra-operative and post-operative fentanyl requirement has been found to be less when magnesium was used peri-operatively in patients undergoing arthroscopic knee surgery with TIVA.[13] In a similar study in patients undergoing cholecystectomy[14] and elective CABG[15] under general anaesthesia also reported same benefit of magnesium. Post-operative tramadol requirement was less when intra-operative magnesium was given to patients undergoing radical prostatectomy under balanced anaesthetic protocol.[16]

The time of the first demand of morphine was significantly longer and the morphine consumption was significantly lower when magnesium was given intra- and post operatively in patients undergoing abdominal surgery.[17] In this study even though the serum magnesium concentration was significantly high in patients received magnesium, the frequency of side effects was similar in the two groups (Magnesium and control).

Magnesium will be better choice than NSAIDs and opioids, especially in patients with respiratory problems or intolerance to NSAIDs for pain management[18] since magnesium is found to act as broncho-dilator.

Even though there are many studies supporting that peri-operative Magnesium sulphate will reduce post-operative pain, it needs further validation. Any way perioperative magnesium supplementation prevents post-operative hypomagnesaemia and decreases the incidence of post-operative shivering.[19]

Magnesium is given to treat eclampsia[20]; it can cause neuromuscular blockade by itself and potentiates neuromuscular blockade by both depolarising and non-depolarising muscle relaxants.[21-22] Magnesium produces systemic and coronary vasodilatation, and decreases reperfusion injuries.[23] It acts as a cardio protective agent by attenuating the increase in intracellular calcium ion flux that accompanies myocardial ischemia followed by reperfusion.[24] It acts as bronchodilator in the management of asthma[25]. Magnesium is relatively harmless, inexpensive molecule and the biologic basis for its potential anti-nociceptive effect is promising.

AIMS & OBJECTIVES:

1. To study the effect of Peri-operative IV Magnesium sulphate on Post-operative pain management in elective lower limb and pelvic surgeries
2. To study the adverse reactions, if any.

SUBJECTS AND METHODS: This study was a double blind, randomised, placebo controlled clinical trial among the patients underwent elective lower limb and pelvic surgeries under spinal anaesthesia which lasted up to 2.5 hours at Christian Medical College Hospital, Ludhiana, Punjab. With the informed consent, 60 ASA-I and II patients aged 18 to 50 years was selected and assigned to two groups ‘M’ group for magnesium and ‘S’ group for placebo(normal saline) randomly.

Exclusion Criteria:

- Narcotics abusers,
- Having any abnormal pre-operative investigation (which include complete blood count, electrocardiogram, renal function test and serum magnesium level),
- Any history of renal diseases,
- Any signs or history indicating existing or previous neuropathy,
- Any history of cardiac disease,
- Any contraindication for spinal anaesthesia.

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All the patients were informed regarding the study, the night before the operation and an informed consent was taken. They were trained regarding the Visual Analogue Scale (VAS) pain scoring.[26] Nil per Orally (NPO) for 6 hours prior to surgery except for pre-medication (Tab. Diazepam 5mg with sip of water 2 hour before surgery) was observed.

Subsequent to the arrival of patient in the operation theatre, heart rate and arterial blood pressure was checked after a resting period of 10 minutes using cardiac monitor and manual sphygmomanometer (Non-invasive) in conjunction with stethoscope. These recordings were considered as baseline values. Standard monitoring (Included heart rate, electrocardiography, pulse oxymetry and blood pressure) was mandatory throughout the surgery. Two intravenous accesses were established, among which one was used to administer IV fluids and other for administering magnesium sulphate.

After pre-loading with 500ml of Ringer's solution over 10-15 minutes, Sub-arachnoid block was performed with the patient in lateral decubitus position under aseptic precaution. 25G Quincke's needle was inserted in the L3-L4 space using midline approach with cephalic bevel. Inj. Bupivacaine 0.5% heavy 2.8ml was used to obtain the block. Soon after the drug administration patient was positioned supine so that bilateral block was achieved. Patient was supplemented with 100% oxygen via face mask.

After a stable block level and appropriate hemodynamic stability, patients were allocated in to two groups; group 'M' for Magnesium and group 'S' for Saline (placebo). Allocation was done by 'slip method'. Sixty slips were made in such a manner that thirty slips had Group 'M' written on them and the other thirty slips with Group 'S'. An anaesthesiologist, who was not involved in the study picked-up one slip, selected the drug accordingly and labelled the bottle with a code. Patient assigned to 'M' group was infused with 500ml normal saline containing Inj. Magnesium sulphate with a dose of 8mg/kg body weight/hour till the end of the surgery. The placebo group 'S' were also received same amount of normal saline. This was prepared by an anaesthesiologist who was not involved in the study in such a manner that no one else were aware of the contents of infusion. He labelled the infusion bottles by code which was assigned to the patient's data sheet. At the end of the study, decoding was done.

Patient's hemodynamic status was maintained such that patient's heart rate and systolic blood pressure were more than 60/minute and 90mm of Hg respectively by appropriate agents like ephedrine/atropine. After surgery patient was transferred to post-anaesthesia care unit and then to post-operation ward after meeting the transfer criteria.

For supplementary post-operative analgesia, following protocol was maintained:

- Patients were assessed for pain with VAS at 3, 6, 12 and 24 hrs. from the time of incision
- Incremental dose of Inj. Morphine was given intravenously whenever a VAS score of >3 out of 10 observed.
- First dose contained 0.05mg/kg of the drug while successive doses had 0.1mg/kg of morphine.

Pain scores, Total morphine consumption and time period were documented. Patient's personal data was kept confidential throughout the study and the patients were given freedom to leave the study just by informing one of the researchers at any point of time.

After completing the entire study the drugs administered was decoded.

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ANALYSIS: Data analysis was done with SPSS software. Quantitative variables are summarized using mean with standard deviation. Qualitative variables are summarized using proportions. The test of significance used were Student's t-test / Mann Whitney-U for comparing the difference in mean between the two groups of non-parametric variables and Chi-square / Mann Whitney U test were used for comparing the categorical data. For comparing the means of more than two groups, ANOVA (Analysis of Variance) was used. A 'P' value of < 0.05 is considered as statistically significant. The Friedman test was used to compare the repeated measures of non-parametric variables.

RESULTS: There was no difference between the groups regarding demographic variable – age (p-value = 0.379), sex (p-value = 0.38), ASA grading (p-value = 0.68) and duration of surgery (p value = 0.057) in this study and so, were statistically comparable.

ANALYSIS OF VAS: The average VAS score in M group at third hour was 0.2+0.61 while that in S group was 2.5+1.14. This difference was statistically significant (p value = <0.0001). Comparison of VAS score at 6th hour also showed a statistically significant difference between two groups with a p-value of 0.001. The average pain score at this point of time was 2.4+1.77 in M group and 4.2+1.5 in S group. The mean VAS score at 12th hour in M group was 3.4+2.06, while that in S group was 4.1+1.08. This difference in VAS score was significant statistically with a p-value of 0.002. 24th hour VAS score difference was also significant with a p-value of 0.002. The mean VAS was 1.9+1.45 in M group and 2.9+1.16 in S group.

Overall the VAS score was less in M group when compared to S group and the difference was statistically significant. The trend in VAS shows an increase in VAS till 12th hour (0.2 at 3rd hour, 2.4 at 6th hour and 3.4 at 12th hour) and then decrease to 1.9 at 24th hour in M group. S group showed highest mean VAS at 6th hour (4.2) and then decreasing pattern (4.1 at 12th hour and 2.9 at 24th hour).

Group	**M group**				**S group**			
Duration	**3**	**6**	**12**	**24**	**3**	**6**	**12**	**24**
Mean	0.2	2.4	3.4	1.9	2.5	4.2	4.1	2.9
Median	0	2	3.5	2	2	5	4.5	2
Standard Deviation	0.61	1.77	2.06	1.45	1.14	1.50	1.08	1.16
Minimum	0	0	0	0	1	2	2	2
Maximum	2	6	7	5	5	6	6	5
Friedman test	54.056				28.612			
df	3				3			
p-value	<0.0001				<0.0001			

Table 1: Comparison of VAS within the two groups

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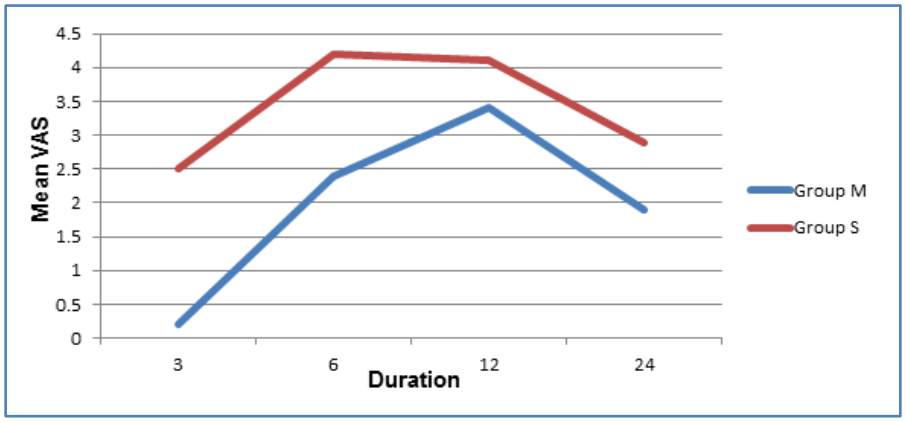

Figure 1: Chart comparing VAS within the two groups

TOTAL DOSE OF MORPHINE: Among 30 patients in M group, only 22 patient required morphine for pain relief while rest eight patients were pain free throughout the observation period. But all patients in group S required morphine for pain relief. The mean and standard deviation of the total dose of morphine used was higher among placebo group (8.53 and 4.051 respectively) compared to the intervention group (7.68 and 3.48 respectively). But this difference was not statistically significant (p-value = 0.43)

Group	No. of pts.	Mean	Standard deviation	Standard error mean
M	22	7.68	3.480	0.742
S	30	8.53	4.051	0.740
p value = 0.43			**t value = 0.79**	**df = 50**

Table 2: Comparison of mean total dose of Morphine between M group and S group

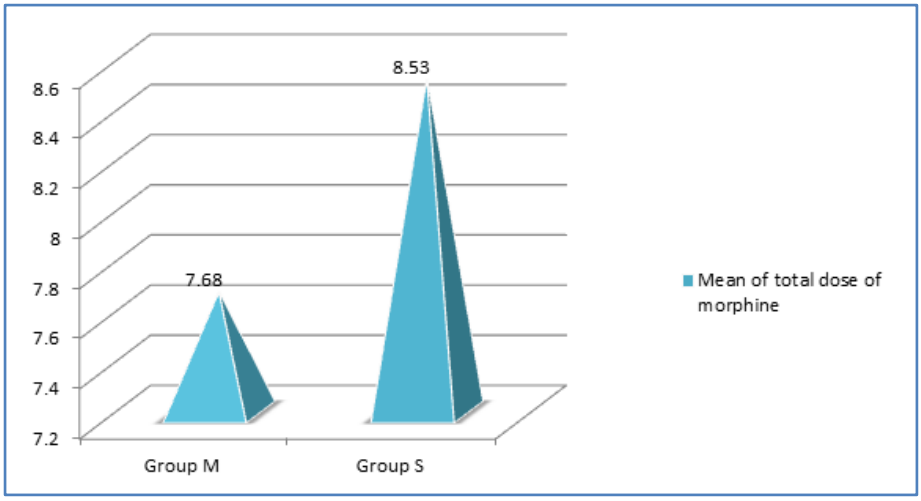

Figure 2: Chart comparing total dose of morphine used between M group and S group

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DURATION FOR THE FIRST REQUIREMENT OF MORPHINE: When we analysed the duration for first analgesic requirement, we found that compared to placebo group, patients in magnesium group had a prolonged pain free period. The mean duration for first dose of morphine was 7 hours and 30 minutes in magnesium group, while that of placebo was 5 hours and 14 minutes. The standard deviations were 3.066 and 2.431 respectively. This was statistically significant with a p-value of 0.01.

Group	No. of pts.	Mean (hours/ minutes)	Standard Deviation
M	22	7.30	3.066
S	30	5.14	2.431
p value = 0.01		**t value = 2.83**	**df = 50**

Table 3: Comparison of time in hours to first dose of morphine between M group and S group

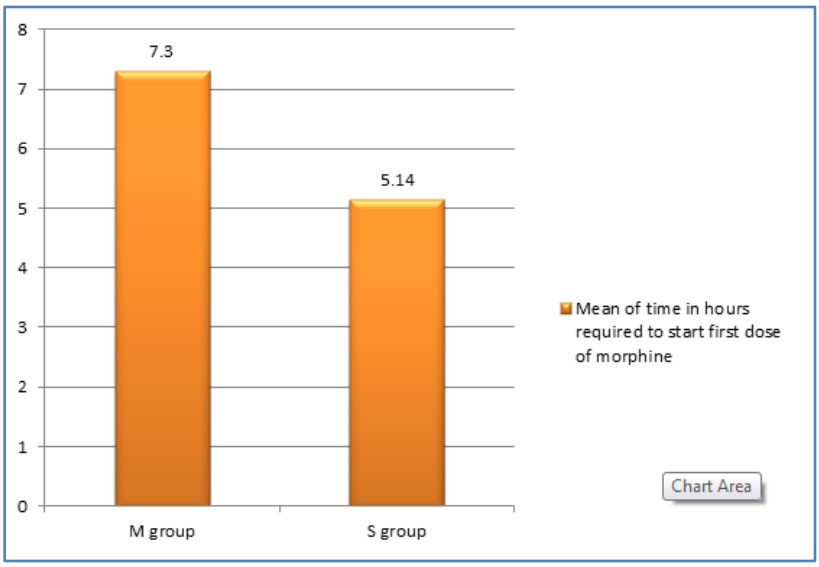

Figure 3: Chart showing time to first analgesic requirement

ADVERSE DRUG REACTION: Statistical comparison of patients developing adverse reaction among magnesium group and placebo group was insignificant with a p-value of 0.27. Forty percent of patients in magnesium group developed adverse reaction while only 26.7% of patient developed adverse drug reaction in placebo group. The relative risk for developing adverse effects was 1.5 times for M group (95% CI of 0.72, 3.13) compared to group S which was also not statistically significant.

When individually analysed the various adverse reactions, the main adverse reaction reported was aggravation of hypotension. 36.7% of patients in magnesium developed hypotension while only 26.7% patients had hypotension in placebo group. This difference was not statistically significant since p-value was only 0.41. Redness (flushing), fever with chills and headache was found in one patient in magnesium group. This was not reported in placebo group. These were not statistically significant (p value of 0.31).

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ANALYSIS ON M GROUP – TOTAL DOSE OF MAGNESIUM USED AND MORPHINE REQUIRED: The mean dose of magnesium infused was 0.87+0.31 mg and the mean dose of morphine consumed by patients in M group was 7.68+3.48 mg. This showed an inverse relation (test statistics = -4.107), which was statistically significant (p-value <0.0001). So more the dose of magnesium used, less the requirement of post-operative analgesia.

	No. of pts.	Mean	Standard deviation
Mg^{2+} used	30	0.87	0.31
Morphine requirement	22	7.68	3.480
p value = <0.0001			**t value = -4.107**

Table 4: Analysis of total dose of Magnesium used and Morphine requirement

DISCUSSION: The result shows that the immediate post-operative period was pain free in magnesium infused patients. This may be because of the analgesic property of magnesium. As this effect wears off, the VAS reading increased to the highest (mean 3.4) in the 12th hour post-operatively. Then it decreased slowly to a mean of 1.9 at 24th hour, since rescue analgesia was given during a VAS of more than 3. In the S group, the VAS slowly increased to a maximum (mean 4.2) at 6th hour, as these patients didn't receive magnesium intra-operatively. Then it decreased at 12th and 24th hour since the rescue analgesia with morphine started earlier than in the M group.

This difference can be attributed to the adjuvant effect of magnesium either to the spinal anaesthesia or to the post-operative analgesia. The analgesic property of magnesium is due to its NMDA antagonistic action. But primary afferent nociceptive input is transmitted via α-amino-3-hydoxy-5-methyl-4-isoxazole propionic acid (AMPA), neurokinin-1 (NK 1), and calcitonin gene-related peptide (C GRP) synapses, whose signals works their way to the thalamus. Glutaminergic (NMDA) synapses do not participate significantly in primary nociceptive transmission, but instead play a crucial role in spinal sensitisation. Accordingly, even after complete NMDA blockade in the spinal cord, primary afferent nociceptive information is transmitted to the thalamus. NMDA antagonists thus have an antihyperalgesic rather than analgesic effect in the spinal cord.[27] This antihyperalgesic property of NMDA antagonist is consistent with the overall VAS pattern in the study which showed significant decrease in VAS score in the magnesium group than the placebo group during whole observation period.

Ryu et al,[28] studied intra-operative IV magnesium in patients undergoing gynaecological procedure under TIVA, reported significantly lower post-operative pain scores. Analysis on studies in patients undergoing general anaesthesia showed that post-operative pain scores was significantly low in magnesium infused group.[14,17,29-30] Studies on peri-operative IV magnesium done in patients undergoing spinal anaesthesia also reported significantly lower mean pain score.[31-33] Post-operative pain scores were also lower when magnesium was infused epidurally.[34-35] Peri-bulbar block along with addition of magnesium to the local anaesthetic also yielded comparatively low pain scores.[36]

Meta-analysis by Murphy et al[37], Kong et al[38] and Lysakowski et al[19] also showed significantly decreased pain scores in magnesium infused group. All these studies point towards the

adjuvant property of magnesium to analgesia to be prominent property than the likelihood of magnesium as adjuvant to spinal anaesthesia. Further this strongly forms the basis for multimodal preventive analgesia.

As stated earlier, the analgesic property of magnesium is attributed to its NMDA antagonistic action. Glutaminergic (NMDA) synapses do not participate significantly in primary nociceptive transmission, but instead play a crucial role in spinal sensitisation. Accordingly, even after complete NMDA blockade in the spinal cord, primary afferent nociceptive information is transmitted to the thalamus. NMDA antagonists thus have an antihyperalgesic rather than analgesic effect in the spinal cord.[27]

Further the blockade of NMDA receptor is the basic principle of preventive analgesia. For a successful preventive analgesia, three critical principal must be followed: (1) The depth of analgesia must be adequate enough to block all nociceptive input during the surgery, (2) The analgesic technique must be extensive enough to include the entire surgical field, and (3) the duration of analgesia must include both the surgical and post-surgical periods. Because of pre-existing sensitization of the nervous system, patients with chronic pain may not respond to this technique. So instead of intermittent boluses of post-operative analgesics, if it was continuous infusion started as multimodal-complete preventive analgesia, the dose of analgesic would have been significantly reduced by NMDA antagonist like magnesium since the primary afferent nociception is effectively blocked.

Its effectiveness also depends on whether the patient was in a state of chronic pain or not prior to the spinal blockade. Since the bulk of this study was in orthopaedic procedures for wounds and fractures, which leads to central sensitisation prior to the spinal block, might be the reason for decreased effectiveness of NMDA antagonist (Magnesium). This is supported by the fact that, 8 patients who were pain free prior to the procedure in M group didn't require any post-operative analgesia.

The first ever study on effect of IV magnesium sulphate on post-operative pain was done by Tramer et al[12] which concluded that post-operative morphine requirement was less in magnesium group. Other studies[13-14,16-18,31-37] also supported the same. But in all these studies the mean difference in total post-operative analgesics used between magnesium group and non-magnesium group were statistically significant ($p<0.05$). The study by Yilmaz et al[15] showed same result as ours, i.e. even though the difference in total morphine use and the frequency of PCA (Patient controlled analgesia) were less in magnesium group, the mean difference was not statistically significant.

Researchers also studied other routes of intra-operative magnesium administration and its outcome. Epidural route was studied by Bilir et al,[34] Yousef-Amr[39] and Farouk[35]. Arcioni et al[40] found that combined spinal and epidural administration of magnesium to be superior to either spinal or epidural administration of magnesium. All of them concluded that magnesium reduced post-operative analgesic requirement. Tauzin-Fin et al[41] hypothesised that infiltration of magnesium along with Ropivacaine reduced analgesic requirement post-operatively. Intra-articular route for administration of magnesium reduced post-operative analgesic requirement was suggested by Farouk and Aly.[42] El-Hamid[36] evaluated magnesium sulphate administered along with local anaesthetic agent in peri-bulbar block and found to be effective.

Studies by Na et al,[29] Benhaj et al[17] and Hwang et al[31] are consistent with our finding that there existed an inverse relation between the dose of magnesium infused and total dose of morphine

required. They say that post-operative serum magnesium was higher in magnesium infused group which consumed less post-operative analgesia. Ko et al[43] found an inverse relation between post-operative CSF magnesium level and post-operative analgesic requirement.

Along with the analgesic property, magnesium was reported to have mild sedative property also. So these patient required post-operative analgesia only in the later stage (Mean duration 7hours and 30 min) as compared to the placebo group (mean duration 5 hours and 14 min). This finding was supported by Benhaj et al,[17] in their study 'Effect of intra and postoperative magnesium sulphate infusion on postoperative pain'. They analysed that the first demand of morphine was significantly longer in M group ($p = 0.03$) and post-operative morphine requirement was high in placebo group ($p = 0.0002$). Similar results were also obtained by Pastore et al[32] and Apan et al.[44]

Yousef and Amr[39] added magnesium to epidural bupivacaine and fentanyl and analysed a similar result i.e. later onset of post-operative pain in magnesium administered patients. Magnesium administered along with local anaesthetic in peri-bulbar block also prolonged the first analgesic requirement. This was put forward by El-Hamid.[36]

It was reported that magnesium causes vasodilatation[45] probably by reducing Ca2+ influx and the competitive inhibition of Mg^{2+} to Ca^{2+} at binding sites of the myosin light chain kinase (MLCK) regulated protein calmodulin. When Mg^{2+} is bound to calmodulin it is unable to stimulate MLCK. This results in lower MLCK activity. Magnesium also regulates nuclear and perinuclear Ca^{2+} in cerebrovascular smooth muscle cells, probably by means of nuclear, ER-Golgi and cytoplasmic L-type voltage membrane regulated calcium channels.[46] This vasodilatory property of magnesium added to cause increased incidence of hypotension in M group (36.7%) compared to S group (26.7%), in which it is purely due to spinal anaesthesia alone.

Even redness, fever / chills and headache seen in one patient in M group can be attributed to this vasodilatory effect of magnesium.

Studies on peri-operative magnesium for its analgesic property show no evidence of increased adverse reaction. Kiran et al[30] reported increased sedation in magnesium treated group while Tramer et al[12] commended as better quality of sleep in magnesium group. Further studies suggest that magnesium reduces incidence of post-operative shivering.[19,28,39,47]

CONCLUSION: From our study we conclude that:

1. Peri-operative IV Magnesium prolongs the first analgesic requirement in patients undergoing spinal surgery. This signifies the role of magnesium in multimodal preventive analgesia.
2. Even though the average dose of morphine required in placebo group was higher than the magnesium infused patients, this difference was not statistically significant.
3. Patients infused with peri-operative magnesium showed a significant reduction of post-operative pain scores (VAS score).
4. There is no significant increase in the incidence of adverse reaction in using peri-operative magnesium sulphate.

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