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Original Article

INTRA-OPERATIVE MAGNESIUM SULPHATE INFUSION DECREASES AGITATION AND PAIN IN PATIENTS UNDERGOING FUNCTIONAL ENDOSCOPIC SINUS SURGERY-A PROSPECTIVE, RANDOMIZED, CONTROLLED AND DOUBLE-BLINDED CLINICAL TRIAL

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ABSTRACT

Objective: To assess the potential role of magnesium sulphate in the reduction of postoperative agitation and pain following functional endoscopic sinus surgery d in the ENT department.

Methods: A prospective, randomized controlled double blinded clinical trial was carried out on 100 patients belonging to both sexes, aged between 18-55 y, posted for functional endoscopic sinus surgery (FESS) under general anaesthesia.

Results: Intraoperative administration of magnesium sulphate in patients undergoing functional endoscopic sinus surgery decreases postoperative agitation and pain intensity; rescue analgesic consumption in the early postoperative period; and the length of stay in PACU.

Conclusion: Intravenous Magnesium sulfate decreases patient agitation and pain after functional endoscopic sinus surgery.

Keywords: Magnesium sulphate, Postoperative pain, Postoperative agitation, Endoscopic sinus surgery

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INTRODUCTION

The primary surgical treatment for chronic rhinosinusitis is functional endoscopic sinus surgery (FESS). There has been a high incidence of postoperative agitation following functional endoscopic sinus surgery (FESS). Postoperative agitation, though short-lived, is potentially harmful to both patients and recovery room staff [1]. An agitated patient requires more number of recovery room staff to control exaggerated movement and has a potential for self-injury by removing intravenous catheters, tubing, oxygen masks and nasal packs [2]. Further, very agitated patients can pose an immediate danger to operating theatre staff. Hence, we have studied the effect of magnesium in prevention and/or amelioration of postoperative agitation in the patients undergoing functional endoscopic sinus surgery (FESS). We have administered magnesium intraoperatively as it has a calming and relaxing effect [3]. It may also provide analgesia and enhance the hypotension required for this type of surgical procedure [4].

Our hypothesis was that magnesium might be beneficial in patients presenting with agitation in the early postoperative period due to the central sedative effect and muscle-relaxing properties. Magnesium Sulphate has potentiating effects on perioperative analgesia and muscle relaxation and, hence can decrease pain and postoperative agitation in patients undergoing functional endoscopic sinus surgery (FESS). Moreover, it has high therapeutic index and is cost-effective**.**

Changes in the concentration of intracellular calcium may lead to persistent changes in the excitability of the dorsal horn cells and, therefore, have an important role for pain perception. Magnesium helps in the regulation of calcium influx into the cell, i.e., "natural physiological calcium antagonism" thereby decreasing the perception of pain. The antinociceptive effect of Magnesium is also due to antagonism of the N-methyl-D aspartate (NMDA) receptors, thereby causing suppression of N-methyl-D-aspartate (NMDA) receptor-induced pain**.**

The main aim of this current study was to investigate the effect of magnesium on postoperative agitation and pain when administered intraoperatively in patients undergoing endoscopic sinus surgery.

MATERIALS AND METHODS

This prospective, randomized, controlled double, blinded clinical trial was conducted at GITAM Institute of Medical Sciences and Research Hospital, Visakhapatnam, between Feb 2021 and May 2022 after approval from the Institutional Ethics Committee.

Written informed consent was obtained from the patients selected for the study.

A total of 100 patients belonging to both sexes, aged between 18-55 y, with American Society of An anesthesiologists (ASA) physical status I, II and posted for functional endoscopic sinus surgery (FESS) under general anesthesia were included in this study.

All the patients were allocated randomly into two group's i.e. Group M and Group N.

Group M

It is the study group.

Magnesium infusion of 30mg/kg was given in the first hour followed by 9mg/kg/h until the end of the surgical procedure after induction and prior to the beginning of surgery.

Group N

It is the Control group.

0.9% normal saline was infused at the same volume and rate after induction and prior to the beginning of surgery.

Methodology

The baseline parameters of both groups, like heart rate, systolic arterial pressure, systolic arterial pressure, diastolic arterial pressure were recorded.

These parameters were monitored continuously and recorded for every 15 min till the end of surgery: Intraoperative heart rate, Spo2, ETCO 2, Mean arterial pressure, systolic blood pressure and

diastolic blood pressure and side effects like hypotension, nausea, vomiting

Pre-anesthetic medication with 0.1 mg/kg Ondansetron and 10 µg/kg Glycopyrrolate was given in the morning on the day of surgery 45 min prior to the beginning of surgical procedure after checking for vital parameters like BP, SpO2, heart rate etc. Preoxygenation with 100% oxygen was given at the rate of 8L/min for 5 min. General anaesthesia was induced using 5 mg/kg Thiopentone sodium. Three minutes after the intravenous injection of 2 mg/kg Succinylcholine, trachea was intubated with an appropriate oral cuffed endotracheal tube, position of endotracheal tube was monitored with capnography and fixed after checking for bilateral air entry. Anaesthesia was maintained with a loading dose of 0.5 mg/kg atracurium, followed by increments of 0.3 mg/kg with an inspired sevoflurane concentration of 2% in a N2O and O2 mixture. The inspired concentration of sevoflurane was decreased to 1.5% after induction of hypotension in both the groups with the aim of maintaining a mean arterial BP (MAP) of 60±5 mmHg to reduce bleeding and improve the surgical field.

After the onset of hypotension, MAP and BIS values were recorded for all the patients. After the completion of surgery, patients were given mephentermine 6 mg intravenously to restore the MAP to the preoperative value.

At the end of surgery, the ulnar nerve was stimulated by means of a nerve stimulator, and the responses of the adductor pollicis were evaluated visually. When patients exhibited spontaneous breathing and a return of two visual twitch responses of the train-of-four (TOF) stimuli in three repeated consecutive series of TOF stimulation, residual neuromuscular block was reversed with Inj. Neostigmine 50-60 µg/kg and Inj. Glycopyrrolate 10µg/kg.

After completion of the surgery, the infusion of magnesiumorsaline was terminated. Patients were extubated after complete recovery when tidal volume was more than 5 ml kg-1, respiratory rate more than 12 breaths min-1, the swallowing and cough reflexes were active, the BIS value was more than 70 and all TOF twitch responses were present without fade.

Patients were then transferred to the recovery room, where they kept under the supervision of an anesthesiology resident who was not aware of the patient's grouping. Duration of surgery and anesthesia, systolic blood pressure (SBP), diastolic blood pressure (DBP), and Heart rate were documented by our colleague who was not aware of patients grouping.

The duration of emergence time was also noted i. e the time taken from the administration of reversal of an aesthesia till eye-opening of the patient. After the patients were shifted to the Post An aesthetic Care Unit, (Recovery room) they were monitored for 1 hour continuously to assess the following parameters:

Postoperative pain

Postoperative agitation

Postoperative heart rate

Mean arterial pressure, systolic blood pressure and diastolic blood pressure

PACU SpO2

PACU stay duration

Any side effects like hypotension, skin flushing, vomiting, or muscle weakness 60 min after admission to PACU, and when agitation and pain score recordings had been completed, injection of diclofenac 75 mg was administered intramuscularly as rescue analgesia for patients whose VAS score was more than 4. Postoperative rescue analgesia was administered after agitation and pain recordings to avoid confounders to the outcome measurement. No. of patients who received rescue analgesia was recorded in both groups. Discharge criteria from PACU were stable vital signs, pain score 2 or less, the absence of nausea and vomiting and a calm and alert patient.

Statistical analysis

Sample size was calculated using SPSS software.

The compiled data was utilized for statistical analysis and expressed as mean±Standard deviation (SD).

Significance of the difference in between two means was assessed using Student (unpaired) T-test.

Significance of difference in between two proportions was assessed using Chi-square test.

p value<0.05 is considered as significant.

RESULTS

Both the groups were similar in their demographic profile and baseline hemodynamic parameters like heart rate and mean arterial blood pressure (table 1).

Table 1: Data demographic

Demographic data	Group M (Study group)	Group N (Control group)	p–value
Age (mean±SD)	31.96±9.63	35.08±11.03	0.1351
Sex (M: F)	26:24	27:23	0.8420
BMI (kg/m^2)	22.32±2.17	22.34±2.16	0.9633
Surgery duration (min)	125.94±5.69	126.34±5.44	0.7201

Demographic data was not significant as p values are>0.05. The two groups were similar in terms of their demographic data, such as age, sex, BMI and duration of surgery.

Table 2: Baseline hemodynamic parameters

Hemodynamic parameter	Group M (Study group)	Group N (Control group)	p–value
Heart rate	78.32±6.50	78.1±6.38	0.8647
MAP	86.0±3.20	84.86±3.36	0.0855

The baseline haemodynamic parameters between the two groups were comparable and not statistically significant as p values are>0.05 (table 2).

Table 3: Comparision of intra-operative heart rate between the two groups

Duration	Group M (Study group)	Group N (Control group)	p-value
0 min	80.92±6.27	80.62±6.15	0.8096
15 min	76.80±6.16	77.06±6.11	0.8326
30 min	73.22±5.40	73.94±5.02	0.4915
45 min	71.12±4.84	71.48±5.10	0.7181
60 min	75.36±4.81	75.63±5.06	0.7087
75 min	77.16±4.93	77.58±5.14	0.6776
90 min	79.20±4.92	79.58±5.14	0.7065

Intraoperative heart rates were similar in both groups and the difference between the two groups was not statistically significant as p values are>0.05 (table 3)

Table 4: Comparison of post-operative heart rate between the two groups

Duration	Group M (Study group)	Group N (Control group)	p–value
0 min	86.2±4.58	97.50±5.17	<0.0001
15 min	84.40±3.44	96.26±4.64	<0.0001
30 min	84.66±2.99	97.16±4.31	<0.0001
45 min	95.5±3.51	97.33±4.02	0.0172
60 min	96.33±3.32	98.22±3.75	0.0089

The post-operative heart rates were significantly lower in Group M compared to Group N as p<0.05 and this difference is highly significant during the 1st 30 min of the post-operative period (p<0.0001) (table 4).

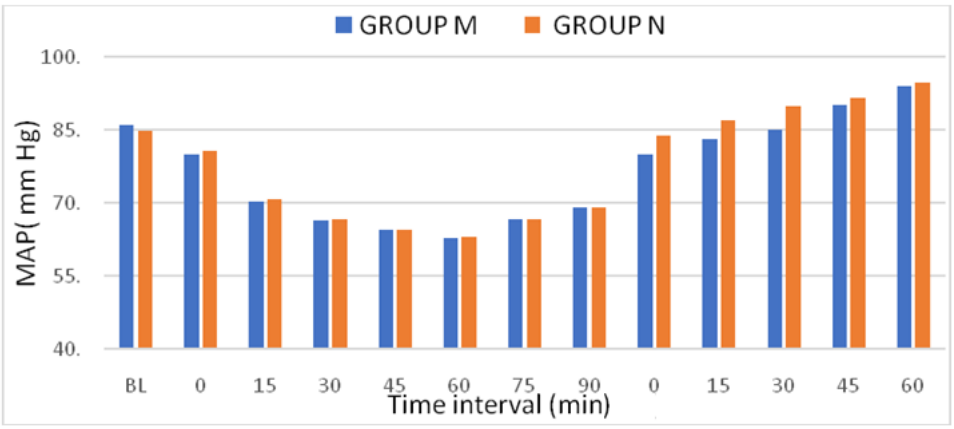


Fig. 1: Comparision of mean arterial blood pressure between the two groups

Intraoperative mean arterial blood pressures were similar in both the groups and the difference between the two groups was not statistically significant as p values are>0.05.

The postoperative mean arterial blood pressures were significantly lower in Group M compared to Group N as p<0.05 and this difference is highly significant during the 1st 30 min of post-operative period (p<0.0001) (fig. 1).

Postoperative RASS scores were lower in Group M (Magnesium) compared to Group N. The post-operative RASS scores between the two groups were statistically highly significant during 1 hour of PACU stay as p values are<0.05, except at 0 min after admission in the PACU (fig. 2).

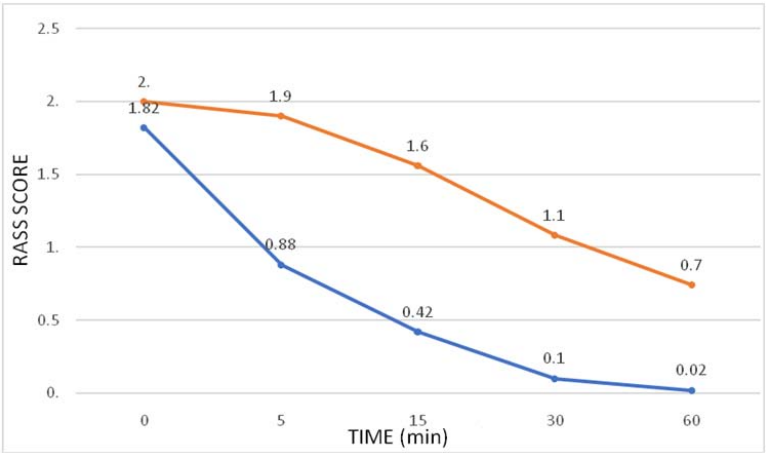


Fig. 2: Comparison of rass scores between the two groups Group m Group n

Table 5: Comparision of post-operative patient characteristics between the two groups in pacu

Patient characteristics	Group M (Study group)	Group N (Control group)	p–value
VAS score (60 min after admission to PACU)	3.56±0.86	5.6±1.38	<0.0001
PACU SpO2	98.76±0.77	98.92±0.78	0.3045
PACU stay time (min)	84.08±16.14	118.44±15.28	<0.0001
Rescue analgesia (yes/no) Y: N	12:38	33:17	<0.0001

Data was expressed as mean±SD, ratio, and absolute numbers. P value<0.05 is considered as significant. VAS scores, PACU SpO2 and PACU stay were analyzed by unpaired t-test (table 5). Number of patients given rescue analgesia was analysed by Chi-square test.

VAS scores were significantly lower in the Group M compared to Group N. (p<0.0001)

PACU stay time was significantly lower in the Group M compared to Group N. (p<0.0001)

Number of patients given rescue analgesia was significantly lower in the Group M compared to Group N. (p<0.0001). PACU SpO2 values between the two groups were similar between the two groups and not statistically significant as p>0.05.

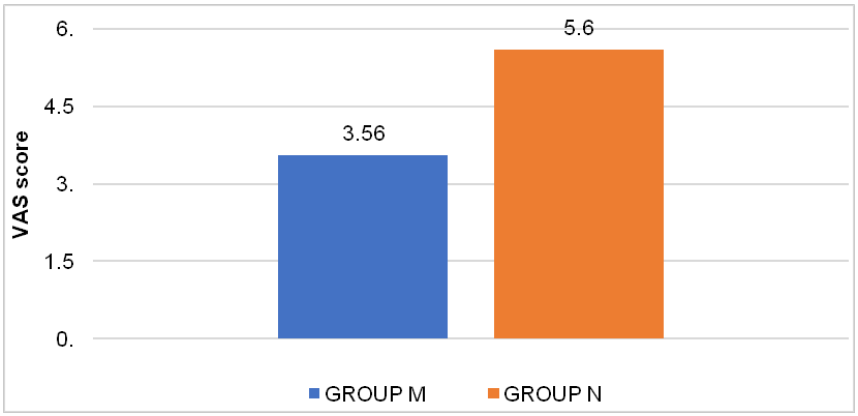


Fig. 3: Comparison of vas scores between the two groups, VAS scores were significantly lower in the Group M compared to Group N, (p<0.0001) (fig. 3)

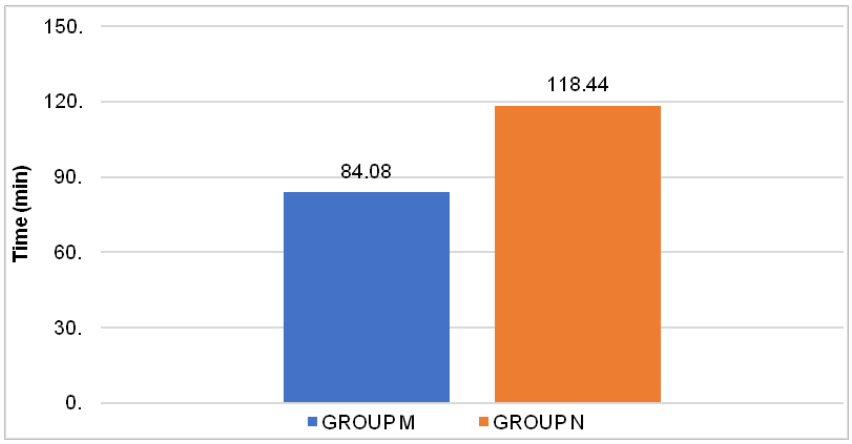
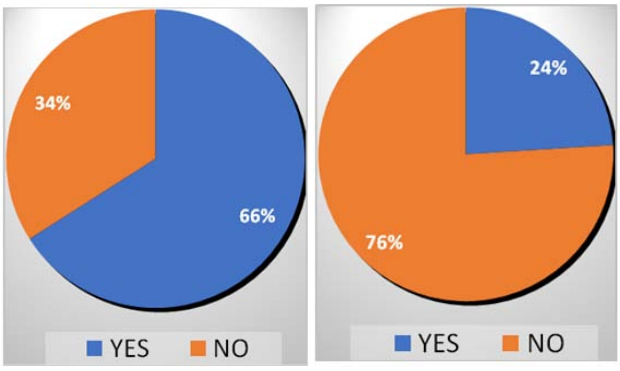


Fig. 4: Pacu stay, PACU stay time was significantly lower in the Group M compared to Group N, (0.0001>p) (fig. 4)



Group M **Group N**

Fig. 5: Rescue analgesia, number of patients requiring rescue analgesia was significantly lower in the Group M compared to Group N (p<0.0001) (fig. 5)

Side effects

We have observed for the side effects i. e postoperative nausea and vomiting (PONV), hypotension, skin flushing and muscle weakness. None of the patients in any of the two groups experienced the above-mentioned side effects.

DISCUSSION

Agitation on emergence from general anaesthesia after nasal surgeries in which intranasal packing is used is common. Emergence agitation following nasal surgeries is a post-anesthetic state that develops in the early phase of recovery from general anaesthesia,

and is characterized by agitation, disorientation, confusion, and possible violent behaviour.

The occurrence of emergence agitation increases the risk for bleeding, falling from operating room table or stretcher in the recovery room, removal of catheters, and self-extubation. Many patients also complain of difficulty in breathing due to acute nasal obstruction (caused by intranasal packing), and is considered as an important factor in the occurrence of emergence agitation.

This may lead to further complications such as desaturation and aspiration of blood. Thus, continuous monitoring, additional medications, and physical restraint may be required which increases the demand on human resources. Emergence agitation[5], could also be partly responsible for high levels of violence reported against healthcare workers in recovery rooms.

Furthermore, postoperative agitation is associated with longer hospital stays and increased morbidity, mortality, and need for institutional stay Early post-anesthesia recovery is a dynamic period during which vital organ systems recover from the effects of anaesthesia and surgery. The return of mental status to preprocedural levels is a critical discharge criterion from the PACU to lower levels of care. Delays in any element of patient recovery can lead to PACU inefficiencies, resulting in a prolonged PACU stay. Profound sedation in the PACU has been associated with increased postoperative adverse events, including respiratory complications.

The incidence of postoperative agitation following nasal surgery is relatively high. Several studies have been conducted in adults to decrease the incidence of emergence agitation after nasal surgeries using different medications. There is some evidence of a neuroprotective effect of magnesium 6. The mechanism by which magnesium reduces postoperative agitation remains to be determined. Magnesium sulphate is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with antinociceptive effects and also inhibits the entry of calcium ions into cells. Intravenous magnesium sulphate has been shown to suppress the increase in brain lactate concentrations and improves the electroencephalographic changes in response to cerebral ischemia. It is possible that magnesium may have decreased agitation by protecting the brain from deleterious effects of prolonged hypotension and other contributing factors.

This present study was conducted to evaluate the effectiveness of intraoperative magnesium sulphate infusion on the incidence of postoperative agitation and pain in nasal endoscopic surgeries.

Hazem E. Elsersy *et al.* [1, 7] in their study, concluded that Intraoperative infusion of magnesium in patients undergoing endoscopic sinus surgery reduced postoperative agitation, pethidine consumption and pain assessed in assessed in the PACU. It also decreased the length of stay in PACU compared with the control group.

M. Abdulatif *et al.* [8] conducted arandomised, controlled, double-blind study and investigated the effects of intra-operative magnesium sulphate administration on the incidence of emergence agitation in patients undergoing adenotonsillectomy using sevoflurane anesthesia. They concluded that Magnesium sulphate reduces the incidence and severity of emergence agitation in patients undergoing adenotonsillectomy usingsevo anaesthesia and is not associated with increased postoperative side-effects or delayed recovery.

Our results were similar to these previous studies as we have found that intraoperative administration of magnesium decreases the incidence severity of postoperative agitation, ameliorates postoperative pain and shortens stay in the PACU in patients undergoing endoscopic sinus surgery. The results of the current study support the use of magnesium for postoperative agitation in adults.

Postoperative pain and hypoxaemia, are major confounders that may cause or result from agitation. In our study, none of the patients of both study and control groups had a reduction in SpO_2, excluding hypoxaemia as a confounding factor for agitation.

Ryu JH *et al.* [9] conducted a randomized, double-blind, prospective study to evaluate the effects of magnesium sulphate on anaesthetic requirements and postoperative analgesia in patients undergoing total I. V. anaesthesia (TIVA). Fifty patients who underwent gynaecological surgery were randomly divided into two groups. Before induction of anaesthesia, the magnesium group (Group M) received magnesium sulphate 50 mg kg (-1) I. V. as a bolus and then 15 mg kg(-1) h(-1) I. V. by continuous infusion. The control group (Group S) received the same amount of isotonic saline. TIVA (propofol+remifentanil) was administered under bispectral index monitoring during anaesthesia induction and maintenance. Rocuronium was administered before orotracheal intubation and during surgery when the train-of-four count was 2 or more. After an operation, patient-controlled analgesia with a solution of ketorolac and morphine was used and the consumption of this solution was recorded. Pain scores at rest and upon movement were evaluated 30 min, 4, 24, and 48 h after surgery. They concluded that I. V. magnesium sulphate during TIVA reduced rocuronium requirement and improved the quality of postoperative analgesia.

Herbert Koinig *et al.* [10] conducted a randomized, double-blind study with two parallel groups to assess the analgesic effect of perioperative magnesium sulphate administration in 46 ASA physical status I or II patients undergoing arthroscopic knee surgery with total IV anaesthesia. The patients received either magnesium sulphate 50 mg/kg preoperatively and 8 mg/kg/hr intraoperative or the same volume of isotonic sodium chloride solution IV. Anaesthesia was performed with propofol (2 mg/kg for induction, 6-8 mg/kg/hr for maintenance), fentanyl (3 µg/kg for induction), and vecuronium (0.1 mg/kg for intubation). Intraoperative pain was treated with bolus fentanyl (l-2 µg/kg). Postoperative analgesia was achieved with fentanyl (0.5 µg/kg) and evaluated using the pain visual analog scale for 4 h. They concluded that, in a clinical setting with almost identical levels of surgical stimulation, IV magnesium sulphate administration reduces intraoperative and postoperative analgesic requirements compared with isotonic sodium chloride solution administration. Magnesium can be an adjuvant to perioperative analgesic management.

Shashi Kiran *et al.* [11] conducted a study to evaluate the efficacy of single dose of intravenous magnesium sulphate to reduce post-operative pain in patients undergoing inguinal surgery. One hundred patients undergoing inguinal surgery were divided randomly in two groups of 50 each. The patients of magnesium sulphate group (Group-I) received magnesium sulphate 50 mg/kg in 250 ml of isotonic sodium chloride solution IV whereas patients in control group (Group-II) received same volume of isotonic sodium chloride over 30 min preoperatively. Pain at emergence from anaesthesia and 2, 4, 6, 12 and 24 h after surgery was evaluated. The timing and dosage of rescue analgesic during first 24 h after operation was noted. They concluded that Preoperative magnesium sulphate infusion decreases postop pain and requirement of rescue analgesia.

In the current study, magnesium reduced pain in non-agitated patients also, indicating that the mechanism of reduction of pain is independent of the reduction of agitation

In our study, we have recorded that in patients treated with magnesium had lesser pain scores compared to the control group. Consumption of rescue analgesia was lower in the patients of magnesium group. Hence magnesium sulphate has also reduced the length of stay in the PACU. These findings were in agreement with the previous studies.

Some of the drugs that are used in anesthetic pre-medication have been shown to increase excitation and agitation. Amongst these, anticholinergic and antihistaminic drugs are incriminated. Substitution of atropine by glycopyrrolate could be of help as the latter does not cross the blood-brain barrier.

Yu *et al.*[12]reported that 55.4% of patients were agitated after ENT surgery; while Kimetal.13 reported a52 % incidence of agitation after the same surgery. The former used premedication of atropine 0.5 mg and midazolam0.1 mg kg-1 and neostigmine–atropine for reversal, whereas the latter used premedication of glycopyrrolate 0.1 mg and midazolam 0.04 mg kg-1, and neostigmine–glycopyrrolate for reversal. It is known that glycopyrrolate does not cross the blood–brain barrier or have any central effect but the

incidence of agitation was not reduced with its use. So, we have used glycopyrrolate instead of atropine as pre medication for the patients in our study to exclude the confounding effect of atropine on agitation.

N. M. Elsharnouby *et al.* [14] conducted a randomized, double-blind, placebo-controlled study to assess the effect of perioperatively administered I. V. magnesium sulphate as a technique of hypotensive anesthesia. Sixty patients (25 female) undergoing functional endoscopic sinus surgery were included in two parallel groups. The magnesium group received magnesium sulphate 40 mg/kg I. V. as a bolus before induction of anesthesia and 15 mg/kg/h by continuous I. V. infusion during the operation. The same volume of isotonic solution was administered to the control group. Intraoperative bleeding was evaluated using a quality scale. They concluded that Magnesium sulphate led to a reduction in arterial pressure, heart rate, blood loss and duration of surgery. Furthermore, magnesium infusion alters anaesthetic dose requirements and emergence time.

In our study, we have also recorded lower average MAP and a lesser amount of intraoperative bleeding in the patients who received Mg sulphate infusion. These findings resemble the clinical outcomes of the previous studies. This would encourage the routine use of magnesium in hypotensive aesthesia as an asoleagentor combined with other drugs.

Strengths of the current study are that the trial is a randomised, double-blinded study with adequate power to support the results regarding the primary outcome. Also, to our knowledge, magnesium has not been implemented so far to prevent or relieve agitation after endoscopic sinus surgery and to shorten the duration of stay in PACU.

Limitations of the study are the assessment of pain only once in the very early recovery period, the lack of measurements of magnesium blood concentrations before and at the end of surgery in each group and the lack of neuromuscular block monitoring intraoperatively. Magnesium interacts with neuromuscular blocking agents by reducing acetylcholine release at the motor nerve terminal. When administered preoperatively, magnesium increases the duration of the neuromuscular block produced by rocuronium15. We used atracurium, which has a different pharmacokinetic profile, and we did not encounter prolonged neuromuscular block after completion of surgery, but our findings would be more robust if the neuromuscular block had been monitored intraoperatively. A large multicentre investigation is required for a dose-response and toxicity study.

CONCLUSION

In conclusion, the intraoperative administration of magnesium sulphate in patients undergoing functional endoscopic sinus surgery decreases postoperative agitation and pain intensity; rescue analgesic consumption in the early postoperative period; and the length of stay in PACU.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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