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ORIGINAL RESEARCH ANESTHESIOLOGY

Effect of magnesium sulphate on propofol requirement in abdominal surgeries under general anesthesia

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ABSTRACT

Background & Objective: Magnesium sulphate ($MgSO_4$) has the potential to be used as a part of balanced anesthesia due to its inherent pharmacological actions. Its judicial use can enhance patient safety. We evaluated the effect of $MgSO_4$ on the total dose of propofol used under bispectral index (BIS) targeted general anesthesia for abdominal surgeries.

Methodology: This prospective randomized controlled trial was conducted on 60 adult patients of either sex, scheduled for elective surgery under general anesthesia. Patients were allocated to two study groups of 30 patients each. In Group I, $MgSO_4$ was administered as 30 mg/kg intravenously (IV) in 100 ml normal saline (NS) over 15 min followed by 10 mg/kg/h infusion intraoperatively. In Group II 100 ml NS was administered over 15 min followed by NS infusion intraoperatively. Anesthesia was induced with propofol, fentanyl, and atracurium in both groups. Intraoperative propofol infusion was started to keep BIS values within 45-55. Data was compared for total dose of propofol used, Ramsay sedation score, recovery characteristics and hemodynamic parameters. Data so collected was statistically analyzed.

Results: The mean quantity of propofol required for induction was less in Group I as compared to Group II, being 1.70 ± 0.19 mg/kg and 2.39 ± 0.58 mg/kg respectively ($P < 0.001$). Group I achieved BIS 60 (59.20 ± 7.63 seconds) faster than Group II (78.36 ± 13.03 sec) ($P < 0.001$). The requirement of propofol for maintenance was less in Group I (4.48 ± 0.95 mg/kg/h) as compared to Group II (6.63 ± 1.65 mg/kg/h) ($P < 0.001$). During recovery, the $MgSO_4$ group needed more time to reach BIS 70 as compared to control group with their mean values being 8.86 ± 1.48 min and 6.88 ± 1.54 min respectively. Response to verbal commands and orientation was also significantly delayed in $MgSO_4$ group as compared to control group ($P < 0.001$).

Conclusion: Magnesium sulphate co-administration with propofol decreases the dosage of propofol to maintain a constant BIS value at 45–55. Sedation and delayed recovery are the notable drawbacks of using magnesium sulphate.

Abbreviations: NMDA - N-methyl-D-aspartate; BIS - Bi-spectral index; HR - Heart rate; MAP - mean arterial pressure

Preregistration: Clinical Trial Registry-India (CTRI/2020/11/029315)

Key words: Magnesium Sulphate; Propofol; BIS Target; Balanced Anesthesia

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1. INTRODUCTION

Magnesium is a drug with multiple clinical applications. Its role in management of eclampsia, torsades de pointes and other intensive care unit settings is well established. It plays fundamental role in various cellular functions. It is the fourth most abundant cation in the body and the second most abundant intracellular cation.[1,2] It activates many of the enzyme systems involved in energy metabolism and acts as a natural calcium antagonist by acting as noncompetitive inhibitor of inositol triphosphate-gated calcium channels.

Amongst the numerous actions of magnesium, the blockade of N-methyl-D-aspartate (NMDA) receptor and calcium channel has an important meaning to anesthesia as by acting on NMDA receptors it has a potential to prevent and treat pain.[2]

Historically, it has been proposed as a general anesthetic and now is recognized as an important part of balanced anesthesia approach. In balanced anesthesia, mixtures of hypnotics and analgesics are used to produce the desired anesthetic effect, thereby decreasing individual dosages and increasing the safety margins.[3]

Propofol is a safe intravenous anesthetic agent but lacks adequate analgesic properties. The higher doses will be required if it is used as single agent for maintenance that have adverse cardiorespiratory effects such as myocardial depression, metabolic acidosis, and impaired platelet aggregation in susceptible population.[4,5] To reduce these harmful effects associated with higher doses, various adjuvants are being studied like magnesium sulphate ($MgSO_4$), clonidine, dexmedetomidine.[3,6-8]

To monitor the adequate depth of anesthesia amongst various monitoring modalities available, bi-spectral index (BIS) is considered as a simple and effective monitoring technique. BIS values of 40–60 are preferred for surgical patients and its values increase with increasing noxious stimuli.[9,10] The BIS has been validated as a measure of anesthetic effect for a number of anesthetic agents, including isoflurane, sevoflurane, and propofol.[11-13]

Although a few studies have demonstrated the beneficial effects of $MgSO_4$ on propofol requirement, but the level of effect of $MgSO_4$ using BIS as a target on intraoperative propofol requirement is less explored. Hence in this present study we assessed the efficacy of $MgSO_4$ in reducing the total dose of propofol using BIS as a target.

2. METHODOLOGY

The present comparative randomized double-blind study was conducted in the department of anesthesiology at tertiary care hospital from March 2020 to September 2021. Approval was obtained from ethics committee (No. ECR/836/Inst./PB/2016/RR-20) and the trial was registered with Clinical Trial Registry-India (No. CTRI/2020/11/029315). A written, informed consent was obtained from all patients.

Patients undergoing surgeries under general anesthesia (GA) and age group between 18-65 y, of either gender, ASA (American Society of Anesthesiologists) grade I and II and scheduled to undergo elective abdominal surgery were enrolled for the study.

Patients with BMI >30, known allergy to magnesium, pregnancy and receiving long term beta blockers, calcium channel blockers, opioids, or magnesium were excluded from the study.

Computer generated randomization was done and 60 patients randomly divided into two groups of 30 patients each. Sealed envelopes were used to conceal randomization. The minimum sample size was calculated taking primary outcome as mean propofol dose taking standard deviation of 20 based on the prior literature with a mean difference of 46 between the samples.[5] Assuming α-error (significance) of 0.05 and power (1- ß) of 99%, the effective sample size came out to be 30 in each group for the comparison.

Pre anesthetic check-up including a detailed history, general and systemic examination was done before surgery. On arrival to the operation theatre, standard ASA monitors were attached and an intravenous line was started.

Group I received $MgSO_4$ 30 mg/kg in 100 ml normal saline (NS) intravenously (IV) as a bolus over 15 min followed by 10 mg/kg/h IV infusion intraoperatively. Group II received 100 ml NS as bolus over 15 min followed by NS infusion intraoperatively. Drug solutions were prepared by an independent consultant not involved in the study.

The level of anesthesia was monitored with bispectral index (BIS) (Covidien BIS LoC channel, Covidien IIc, 15 Hampshire Street, Mansfield, MA 02048 USA). The

target BIS range was 45-55 for surgical anesthesia. Prior to administering study drug, ECG; BIS value; SpO_2; level of sedation using Ramsay sedation scale, heart rate (HR) and mean arterial pressure (MAP) were noted as a baseline values after 5 min of stabilization of the patient.

After preoxygenation for 3 min, patients were administered 1 µg/kg of fentanyl citrate IV. They were induced by injection propofol, administered at a rate of 20 mg per 5 sec until BIS was below 60. The time required as well as the dose of propofol consumed were noted. Endotracheal intubation was facilitated by muscle relaxant atracurium sulphate (0.5 mg/kg IV). Anesthesia was maintained by nitrous oxide and oxygen (50% + 50%) along with propofol infusion, started at the rate of 200 µg/kg/min and titrated to maintain BIS in the range of 45-55. BIS was monitored continuously and propofol infusion was increased or decreased by 20 µg/kg/min if the BIS value was out of range for more than 10 sec.

Dose adjustment of fentanyl was based on clinical signs and hemodynamic measurements. Signs of inadequate analgesia, defined as an increase of heart rate and MAP of more than 20% of baseline, were managed by a bolus dose of fentanyl 0.5 µg/kg (if BIS was within the recommended range of 45-55). In the event of bradycardia (HR < 50 bpm) injection atropine 0.5 mg IV bolus was given; and hypotension (MAP < 20% of preinduction value) was managed with IV fluid boluses or injection mephenteramine 6 mg bolus if needed. Muscle relaxation was achieved by intermittent bolus doses of atracurium sulphate. The patients were mechanically ventilated to keep $EtCO_2$ between 35 and 40 mmHg. Normothermia was maintained.

At the end of the surgical procedure (skin closure), all the infusions were stopped. Time for BIS to rise to 70 was recorded (termed as BIS 70). The time elapsed between stoppage of propofol infusion and a BIS value of 70 was considered as the recovery time. Residual neuromuscular block was reversed by neostigmine (0.03-0.07 mg/kg) and glycopyrrolate (0.01 mg/kg). Tracheal extubation was performed and time to response to verbal commands (spontaneous eye opening), and orientation time (to recollect name, date of birth and location) were noted.

Total use of propofol was recorded. The amount of propofol infused excluding the bolus dose was divided by the patient's body weight and total infusion time. In each patient μg/kg/min indicates unit of mean propofol infusion rate during the entire infusion period.

Heart rate, MAP, SpO_2 were also recorded throughout the surgical procedure at an interval of 5 min for 30 min and then 10 min till the end of surgery.

The patients were observed for any adverse effects throughout the procedure and postoperatively. At 30 min postoperatively, RSS was noted in the recovery room.

Statistical analysis

After completion of study, observations obtained were tabulated and analysed using statistical methods. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21.0 version for Microsoft Windows. Data was described in terms of range, means + standard deviation (+ SD), frequencies (number of cases) as appropriate. Comparison of quantitative variables between the study groups was done using Student's t-test and Mann-Whitney test. For comparing categorical data, chi square test was performed. A probability value (P value) less than 0.05 was considered statistically significant and P > 0.05 was considered insignificant.

3. RESULTS

A total of 60 patients were enrolled in the study with 30 patients in each group. The demographic variables, e.g., age, weight, height, gender distribution, body mass index (BMI) and ASA grade were similar in both the groups (P > 0.05) (Table 1). Both the groups were also comparable as regards to duration of surgery (Table 1).

The mean requirement of propofol for induction and for maintenance was significantly lower in Group I compared to Group II (Table 2). Table 2 also shows that time achieve BIS 60 was significantly less in Group I.

Table1: Comparative demographic variables in two groups

Variables	Group A	Group B	P-value
Age (y)	49.73 ± 9.54	48.50 ± 12.48	0.669
Weight (kg)	69.33 ± 4.01	68.47 ± 4.87	0.455
Height (cm)	164.53 ± 5.53	165.37 ± 5.25	0.552
BMI (kg/m2)	25.51 ± 1.93	25.06 ± 1.87	0.370
Gender (Male/ Female)	17/13	19/11	0.598
ASA Grade (I/II)	16/14	14/16	0.606
Duration of Surgery in min	78.33 ± 10.20	75.17 ± 12.28	0.282

Data presented as Mean ± SD or numbers; P > 0.05 not significant

Table 2: Propofol requirements and induction Characteristics: p value < 0.001, highly significant

Variables	Group I	Group II	P-value
Propofol required during induction (mg/kg)	1.70 ± 0.19	2.39 ± 0.58	0.000
Time to achieve BIS 60 (sec)	59.20 ± 7.63	78.36 ± 13.03	0.000
Propofol required during maintenance (mg/kg/h)	4.48 ± 0.95	6.63 ± 1.65	0.000

Data presented as Mean ± SD; P < 0.001 highly significant

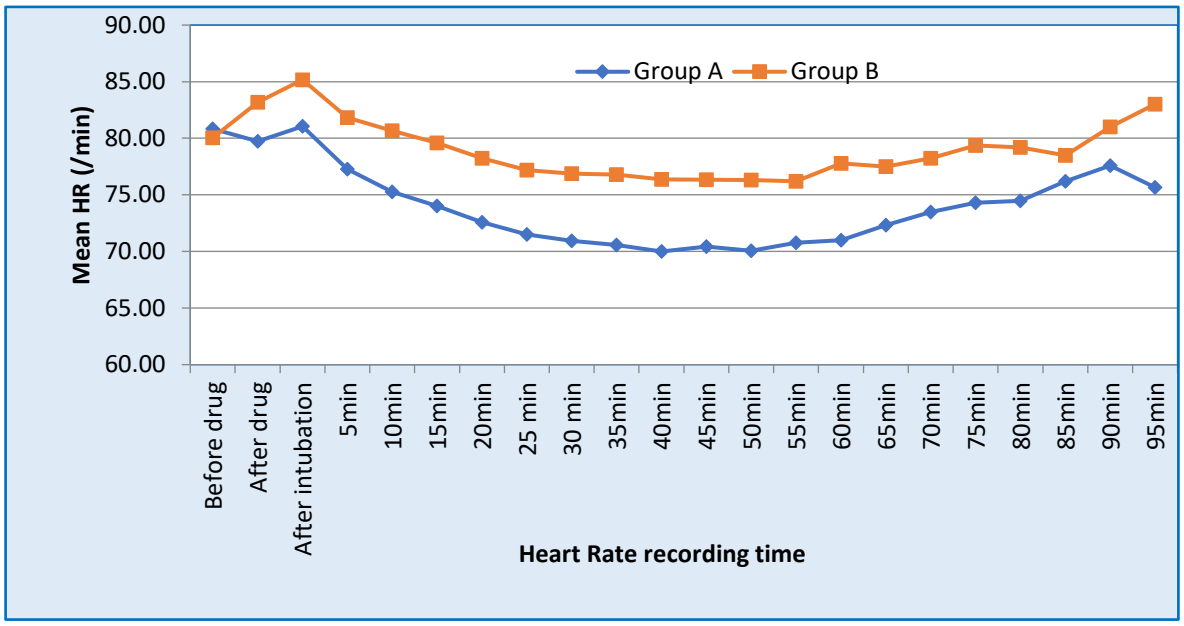

Figure 1: Intraoperative mean heart rate (per min)

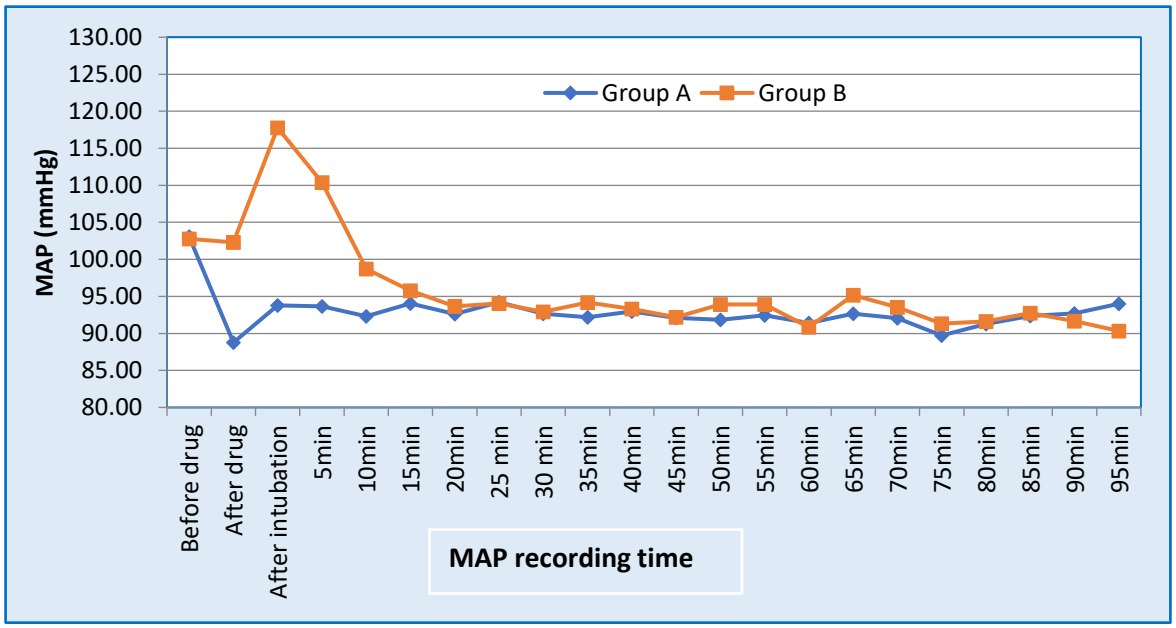

Figure 2: Intraoperative mean arterial pressure at various time intervals in study groups (mmHg)

Table 3: Recovery characteristics; P < 0.001, highly significant

Variables	Group I	Group II	P-value
Response to verbal command (min)	10.33 ± 1.44	7.83 ± 1.41	0.000
Time for orientation (min)	11.03 ± 1.33	8.94 ± 0.93	0.000
Ramsay Sedation Score, 30 min postop	2.37 ± 0.49	2.47 ± 0.51	0.441

Data presented as Mean ± SD; P < 0.001 highly significant

Hemodynamic parameters in regards to heart rate and MAP was comparable between the two groups at all the time interval as shown in Figure 1 and 2.

During recovery the patients of Group I took more time to verbal response as well as time to orientation (Table 3). Patients in Group I were also more sedated as compared to Group II (Table 3).

4. DISCUSSION

Role of perioperative physicians has always been to ensure patient safety along with adequate anesthesia depth for surgical exposure without any intraoperative awareness and hemodynamic compromise. To achieve this goal anesthesiologist are always in look out for newer agents or newer techniques. Magnesium is not a new drug but its actions at NMDA receptor antagonist and as calcium channel blocker make it an alluring drug for pain relief. NMDA receptor antagonists are best administered before the generation of noxious stimuli in order to prevent central sensitization.[1]

We aimed to titrate the dose of propofol to achieve a BIS range 40–50, which falls within the recommended range for GA.[14] We incorporated the use of $MgSO_4$ with BIS monitoring to get more objective evidence based values.

The mean amount of propofol required for induction, maintenance and time taken to achieve BIS 60 was lower in $MgSO_4$ group as compared to control group ($P < 0.05$) (Table 2). This is well explained by the inhibition of NMDA receptors and reduced uptake of calcium at pre synaptic receptors by magnesium. .

The results of present study correlate well with a study done by Ray Manjushree et al. in terms of reduction in propofol requirement for induction as well as maintenance of GA and lesser time taken to achieve BIS 60 with the use of $MgSO_4$. They conducted a randomized, placebo-controlled, double-blind study to assess the effect of intravenous clonidine and $MgSO_4$ on intraoperative hemodynamics, anesthetic consumption and postoperative recovery. Magnesium group received $MgSO_4$ 30 mg/kg as a bolus before induction and 10 mg/kg/h by infusion, clonidine group received clonidine 3 µg/kg as a bolus before induction and 1 µg/kg/h by infusion intraoperatively. Requirement of propofol was found to be significantly lower in clonidine group and Magnesium group compared to placebo group, both for induction of anesthesia and for maintenance ($P < 0.001$).[15]

The overall reduction in propofol consumption in our study also correlated well with the study conducted by Walia Chiteshwar et al. who did a controlled trial on propofol sparing effect of dexmedetomidine and $MgSO_4$ during BIS targeted anesthesia. They concluded that pre-treatment with dexmedetomidine and magnesium significantly reduced the induction dose of propofol.[5]

Gupta K et al. and Yoldas et al. also demonstrated that $MgSO_4$ has anesthetic, analgesic and muscle relaxation effects and significantly reduces the drug requirements of propofol.[16,17]

During recovery it was noted that the $MgSO_4$ group needed more time to reach BIS 70 as compared to control (Table 3). Also, response to verbal commands and time for orientation was significantly raised in $MgSO_4$ group (Table 3) as compared to control group ($P < 0.001$). $MgSO_4$ causes delay in recovery possibly due to its central nervous system depression properties.

Olgun et al. evaluated the effects of $MgSO_4$ infusion at 40 mg/kg on anesthetic requirement, early recovery and postoperative analgesia in desflurane-remifentanil-based, balanced anesthesia and demonstrated that although perioperative use of $MgSO_4$ reduced the requirement for anesthetic drugs and Visual Analogue Scale (VAS) pain scores, but significantly increased recovery time.[18] The overall delay in recovery parameters in our study also correlates with the study by Ray Manjushree et al.[15]

After administration of drug, magnesium group showed significantly lower levels of mean heart rate as compared to control group (Figure 1). During initial periods the decrease in heart rate was highly significant ($P < 0.001$) and towards the end it was less significant ($P < 0.05$). Mean arterial pressure (MAP) also showed a similar trend and there was pronounced fall in MAP during initial periods of time after administration of $MgSO_4$ (Figure 2). But no patient had bradycardia or episode of

hypotension that required pharmacological intervention. This hemodynamic effect of $MgSO_4$ could possibly be due to hypotension directly by vasodilatation and indirectly by sympathetic blockade. Similar trend has also been shown by study done by Yoldas et al.[17]

5. LIMITATIONS

This study was a small attempt to demonstrate the reduction in requirement of propofol in abdominal surgeries keeping BIS as objective measure. However, we did not assess analgesic requirement and muscle relaxant potentiation in this study. It would have been more interesting if we avoided use of nitrous oxide as well and did the study solely on propofol for maintenance. Another limitation in our study is that we did not measure perioperative plasma concentration of magnesium. Correlation between magnesium plasma level and BIS values can be useful in a future study for more accurate assessment of the direct central effect of $MgSO_4$ guided by the BIS.

6. CONCLUSION

Magnesium sulphate is a cost-effective drug which can be used as an adjuvant in general anesthesia. When co-administrated with propofol, it decreases propofol dosage to maintain a constant BIS in value at 45–55 along with hemodynamic stability. Sedation and delayed recovery were the notable drawbacks.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

HK, AS: Concept, conduction of the study work and manuscript preparation

VP: Conduction of the study work and writing of the manuscript

AS, KK: Data analysis, interpretation, and manuscript editing

PS: Data analysis, manuscript editing

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