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ORIGINAL RESEARCH

# Lidocaine versus magnesium sulfate infusion during isoflurane anesthesia for brain tumor resection, effect on minimum alveolar concentration reduction guided by bispectral index: a prospective randomized controlled trial

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## Abstract

**Objective**: Goals of neuro-anesthesia include smooth induction, stable perioperative hemodynamics, early and quiet recovery with adequate analgesia. Intraoperative use of co-sedatives allows reduction of anesthetic agents consumption while maintaining a desirable depth of anesthesia. Many drugs like opioids and dexmedetomidine had been studied in different surgeries. Using such drugs enhances rapid recovery for early postoperative assessment and detection of complications.

**Methods**: This study enrolled 50 adult patients undergoing supratentorial brain tumor surgery. Patients of the lidocaine group (group L) received 1.5 mg.kg$^{-1}$ of lidocaine as a loading dose over 10 min before induction of anesthesia and followed by infusion at a rate of 1.5 mg.kg$^{-1}$.h$^{-1}$. Patients of the magnesium group (group M) received 30 mg.kg$^{-1}$ of magnesium sulfate as a loading dose over 10 min before induction of anesthesia and followed by infusion at a rate of 10 mg.kg$^{-1}$.h$^{-1}$. Depth of anesthesia was guided by bispectral index in a range of 50 $\pm$ 2, with the primary outcome objective, minimum alveolar concentration reduction of inhaled isoflurane.

**Results**: No significant difference was found regarding patient demographics, basal hemodynamic data, and anesthesia duration. The used isoflurane concentration at the matching time points (every 15 min intraoperatively) and the total dose of muscle relaxant (160 $\pm$ 15 mg, 175 $\pm$ 18 mg respectively, $p$ 0.003) were statistically lower in group M than in group L. The time required for recovery was statistically shorter in group M than in group L (5.1 $\pm$ 0.99 min vs 9.8 $\pm$ 1.9 min, respectively, $p$ 0.00).

**Conclusion**: Compared to lidocaine infusion, magnesium sulfate ($MgSO_4$) infusion during anesthesia for brain surgery resulted in lower anesthetic consumption, muscle relaxant requirement, a shorter recovery time, and a better postoperative pain profile. $MgSO_4$ can be used effectively as a co-sedative adjuvant with superior clinical properties than lidocaine infusion.

## Keywords

Magnesium; Lidocaine; Bispectral index; Supratentorial neoplasm; Deep sedation; Anesthetics; Inhalation

## 1. Introduction

Brain tumors constitute the majority of neurosurgical conditions that present for elective operations. The goals of neuro-anesthesia are to enhance smooth induction, maintain stable perioperative hemodynamics while keeping appropriate cerebral blood and oxygen supply with optimal operative conditions [1, 2].

Early and quiet recovery from anesthesia is desirable for early screening of potential complications, such as bleeding, ischemia, cerebral herniation, neurological deficits, and tension pneumocephalus. The residual effect of anesthesia may give the false impression of a neurological deficit or obscure early diagnosis of an impending intracranial problem. So, reduction of anesthetic drug consumption while maintaining the desired depth of anesthesia appears of great value. To achieve these targets, the use of adjuvant drugs was explored in literature with variable results [2, 3].

Lidocaine has a central analgesic and sedative effect through blocking sodium channels and inhibition of ion transport and action potential propagation. The mechanism of lidocaine's action involves its binding to sodium channels and its interaction with the general anesthetic agents resulting in a synergic effect. Lidocaine has also been shown to possess an anti-inflammatory


  

action and to prevent central hyperalgesia. Perioperative systemic administration of lidocaine was associated with lower anesthetic agent consumption and reduced postoperative pain scores and analgesic requirements [4, 5].

Similarly, Magnesium sulfate was used in combination with anesthetic drugs to potentiate their actions, and minimize their requirements [6]. Magnesium sulfate is an N-methyl-D-aspartate (NMDA) receptor antagonist with potential analgesic, sedative, and anticonvulsant properties. Furthermore, it has been postulated to have both cardiac and neurological protective effects [7, 8].

In this trial, we aimed to compare the effects of intraoperative infusion of lidocaine to the infusion of magnesium sulfate regarding intraoperative consumption of inhalational anesthetics during bispectral (BIS) guided general anesthesia for brain tumor surgery (primary objective). Secondary objectives included hemodynamics stability, muscle relaxant consumption, recovery profile and postoperative pain.

## 2. Methods

This study was approved by the ethical committee of Mansoura faculty of medicine in the form of the institutional research board (IRB #R 20.06.913, July 5-2020), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrolment at the Pan African Clinical Trial Registry system (PACTR 202007774954789, July 17-2020).

After obtaining the ethical approval, trial registration, and consent from all patients to participate, the study was conducted on adults of both sex, ASA I or II with the age range of 18–65 years, Glasgow coma score (GCS) $\geq$ 14 undergoing supratentorial brain tumor surgery. Fifty patients completed the study protocol, which adheres to the applicable CONSORT guidelines (Fig. 1). Exclusion criteria included patient refusal, preoperative major cardiopulmonary disorders, sinus bradycardia, heart block, hepatic or renal dysfunction, and known allergy to used drugs. Intraoperative major bleeding, hemodynamic instability necessitating interruption of the study infusions were also excluded from the study. With the closed envelope technique, a random number generator allocated the patients into two groups based on the co-sedative regimen: 25 for the magnesium group (group M), 25 for the lidocaine group (group L). According to our policy, the preoperative patient assessment included medical and surgical history taking, GCS assessment, electrocardiography (ECG), Echocardiography, complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), and coagulation profile.

In the operative suite, patients were connected to monitor (General Electric-Datex B850, USA) for ECG, non-invasive blood pressure (NIBP), peripheral oxygen saturation ($SpO_2$) monitoring. A 20-gauge venous catheter was inserted in the non-dependent arm. All patients received intravenous 40 mg of pantoprazole (Zurcal 40 mg, AUG pharma, Spain), 8 mg of dexamethasone (Dexamethasone, Sigmatic, Egypt), and 3 mg of midazolam (Midathetic, Amoun pharmaceuticals). Ringer acetate infusion started at a rate of 5 $mL.kg^{-1}.h^{-1}$ and continued as a maintenance fluid till the end of surgery.

According to the randomization number received with the patient's file in a closed envelope, a trained independent anesthesiologist prepared study medication in covered syringes labeled by randomization number either for loading or for continuous infusion. Patients group L received lidocaine (1.5 $mg.kg^{-1}$) as a loading dose over 10 mins before induction of anesthesia, followed by infusion at a rate of 1.5 $mg.kg^{-1}.h^{-1}$. Patients of group M received magnesium sulfate (30 $mg.kg^{-1}$) as a loading dose over 10 mins before anesthesia induction, followed by infusion at a rate of 10 $mg.kg^{-1}.h^{-1}$. Each drug's loading dose was prepared in a 50-cc syringe and given at a rate of 300 $mL.h^{-1}$ in the operative suite. During the loading dose infusion, patients were kept attached to basic monitors and continuously observed for any related side effects.

In the operating room, patients were monitored for ECG, NIBP, end-tidal $CO_2$, and $SpO_2$. Leads of bispectral index (BIS) were placed at the correct place and connected to monitor the depth of anesthesia. According to previously prescribed doses, the infusion of the study medication was initiated at a rate of 0.1 $mL.kg^{-1}.h^{-1}$, in a new labelled 50-cc syringe containing either lidocaine (15 $mg.mL^{-1}$) or $MgSO_4$ (100 $mg.mL^{-1}$).

Anesthesia was induced using propofol 1–2 $mg.kg^{-1}$ (Diprivan, Fresenius Kabi), fentanyl 1 $\mu g.kg^{-1}$ (fentanyl Hameln, Hameln pharmaceuticals, Germany), atracurium 0.6 $mg.kg^{-1}$ (Atrabesylate, Egypharm, Egypt). A proper-sized armored endotracheal tube was inserted and fixed in place after confirmation of correct positioning guided by capnography and lung auscultation. Patients were ventilated using (GE Datex-Ohmeda Aisys, USA) a closed-circuit ventilator, with volume-controlled ventilation mode to keep $EtCO_2$ (30–32 mmHg).

Anesthesia was initially maintained using isoflurane 1–1.2% in 40% oxygen air gas mixture with the fresh gas flow of 2 L/min, while isoflurane concentration was managed every 15 mins to keep BIS 50 $\pm$ 2. Top up the dose of atracurium 0.1 $mg.kg^{-1}$ was given on needs guided by the train of four (TOF) monitoring to keep no more than two twitches present (>80% block). Fentanyl infusion 0.5 $\mu g.kg^{-1}.h^{-1}$ and 1 gm of paracetamol were infused as a part of the multimodal analgesia technique. Before surgery, two large peripheral lines and a 7.5-G central line catheter were inserted and secured in place. A suitable size urinary catheter was inserted for urine output collection.

The researcher anesthesiologist did the intraoperative anesthetic management, monitoring, and data recording. The collected data included the hemodynamic parameters, BIS readings, and inspired isoflurane concentration every 15 min till the end of surgery. When cautery used by the surgeon, BIS reading was taken at pointed times in interval at least one minute from cautery used to avoid reading fallacy from electrical signals of cautery. Hemodynamic parameters were allowed to swing in a 20% range of basal data. Any increase in heart rate or blood pressure above the acceptable range was managed by deepening anesthesia by increasing isoflurane concentration (keeping BIS range 50 $\pm$ 2) or increasing fentanyl analgesics infusion rate. Other drugs like beta-blocker can be used in resistant situations after ensuring adequate depth of anesthesia and analgesia levels. On the other hand, significant bradycardia or hypotension were managed by decreasing anesthetics concentration (keeping BIS range 50 $\pm$ 2), using vasopressor

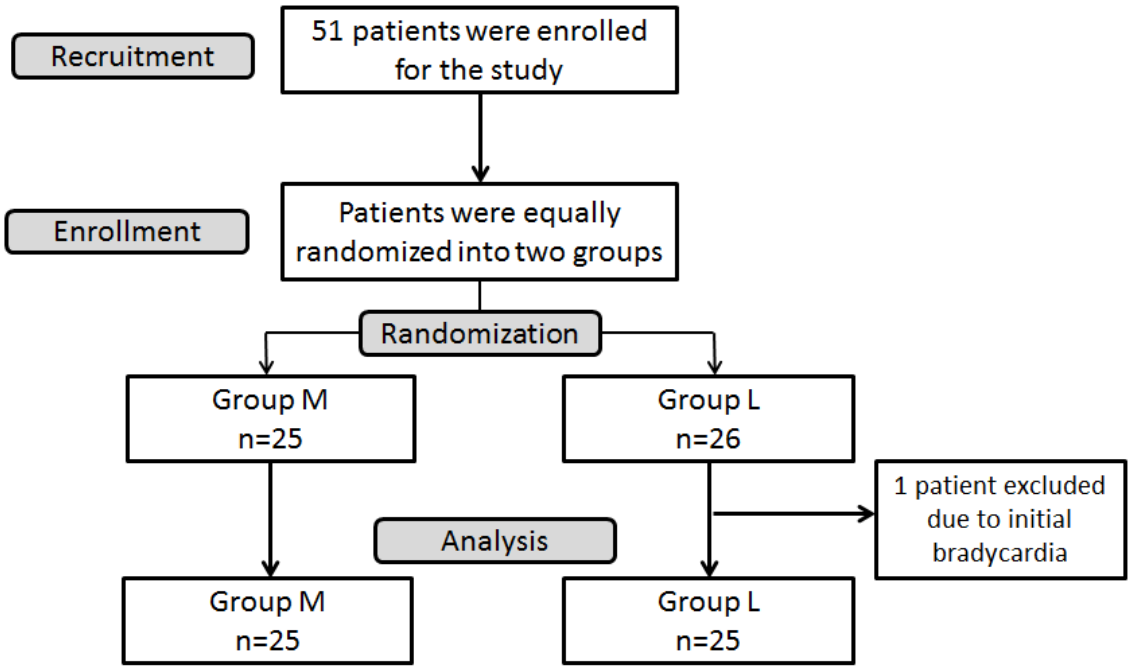


**FIGURE 1. Consort flow diagram for the study.**

drugs or fluids and blood transfusion according to the clinical situation and blood loss.

After completing the surgical procedure, including tumor excision, hemostasis, closure of the dura layer, putting bone segments, and closing subcutaneous layers, the infusion of the study drugs was stopped. Inhalational isoflurane anesthesia was turned off at the final skin suture. Muscle relaxation was reversed using neostigmine 0.05 mg.kg$^{-1}$ plus Atropine 0.02 mg.kg$^{-1}$ when second twitch TOF appears (<90% block), and extubation was performed after fulfilment of awake extubation criteria. The recovery time (time elapsed from turning off inhalational isoflurane anesthesia till awake extubation) and the total muscle relaxant consumption were recorded.

In a post-anesthesia care unite (PACU), patients were observed for hemodynamics, sedation score using Richmond agitation sedation score (RASS) and pain assessment by visual analogue score (VAS). Patients were shifted to the intensive care unit (ICU) for close postoperative monitoring and management. Postoperative analgesia was maintained by paracetamol, 1 gm every 8 hours, and rescue opioids if VAS is more than 4. The postoperative data, including hemodynamics and VAS for early six postoperative hours, were collected by an ICU nurse staff blinded to study groups.

## 3. Sample size and statistical analysis

A pilot study was conducted, including five patients in each study group to calculate the mean isoflurane concentration used during brain tumor surgery in our centre (0.78 ± 0.19 vs 0.64 ± 0.03). G*power software version 3.1.9.2 was utilized to detect the required sample size. A sample size of 46 patients was found sufficient a study power of 90% and an alpha error of 0.05. Cases involved in the pilot study were included in the total sample size. Additional four patients per group were recruited to compensate for dropouts reaching a total sample size of 50 patients. Perioperative data were tabulated and analyzed using IBM SPSS software version 22. Continuous data were presented as mean SD or median IQR according to the normality of distribution. Nominal and categorical data were presented as numbers and percentages. Independent sample *T*-test, Mann-Whitney test or chi-square test was utilized to detect statistical differences between the studied groups.

## 4. Results

This study enrolled 50 patients scheduled for elective supratentorial brain tumor surgery, presented in Fig. 1. Patient demographics, basal hemodynamic data, preoperative respiratory rate, total muscle relaxant consumption, isoflurane consumption, mean isoflurane concentration and duration of anesthesia are presented in Table 1. The total muscle relaxant dose was statistically lower in group M than the dose required in group L (160 ± 15 mg, 175 ± 18 mg, respectively, $p$ 0.003). Also, isoflurane consumption was statistically lower in group M than group L (20.99 ± 3.36 mL, 27.78 ± 6.18 mL, $p$ 0.001). Mean isoflurane concentration (allover anesthesia duration) was statistically lower in group M than group L (0.73 ± 0.06, 0.93 ± 0.13, $p$ 0.001), while other parameters show no statistically significant difference between the studied groups. None of the patients showed any side effects related to the loading doses of the study drugs before transfer to OR.

Perioperative hemodynamic measurements (HR, MAP) are illustrated in Fig. 2. Patients HR and MAP were lower in group M than group L throughout anesthesia, reaching statistical significance for HR ($p$ 0.04, 0.02, and 0.03) time points at 30, 135, 180 mins correspondingly.

The depth of anesthesia measured by the BIS against the

**TABLE 1. Patients basal data and perioperative characteristics. Data are presented as mean ± SD or numbers.**

| | Group L | Group M | *p* |
|---|---|---|---|
| Age (years) | 39 ± 15 | 40 ± 16 | 0.81 |
| BMI (kg/m$^2$) | 24 ± 2.6 | 24 ± 3.1 | 0.83 |
| Gender (M/F) | 9/16 | 12/13 | 0.28 |
| Basal HR (bpm) | 83 ± 7 | 79 ± 6 | 0.09 |
| Basal MAP (mmHg) | 96 ± 5.7 | 94 ± 6.8 | 0.19 |
| Basal $SpO_2$% | 99 ± 0 | 98 ± 0.2 | 0.3 |
| Basal RR | 13.5 ± 1.4 | 12.7 ± 1.7 | 0.09 |
| Anesthesia duration (minutes) | 285 ± 36 | 279 ± 34 | 0.55 |
| Total muscle relaxant dose (mg) | 175 ± 17.7 | 160 ± 15.3 | 0.003* |
| Isoflurane consumption (mL) | 27.78 ± 6.18 | 20.99 ± 3.36 | 0.001* |
| Mean isoflurane conc. (%) | 0.93 ± 0.13 | 0.73 ± 0.06 | 0.001* |

*BMI, body mass index; M, male; F, female; HR, heart rate; bpm, beat per minute; $SpO_2$, peripheral oxygen saturation; RR, respiratory rate; conc., concentration.*
**p-value is significant if less than 0.05.*

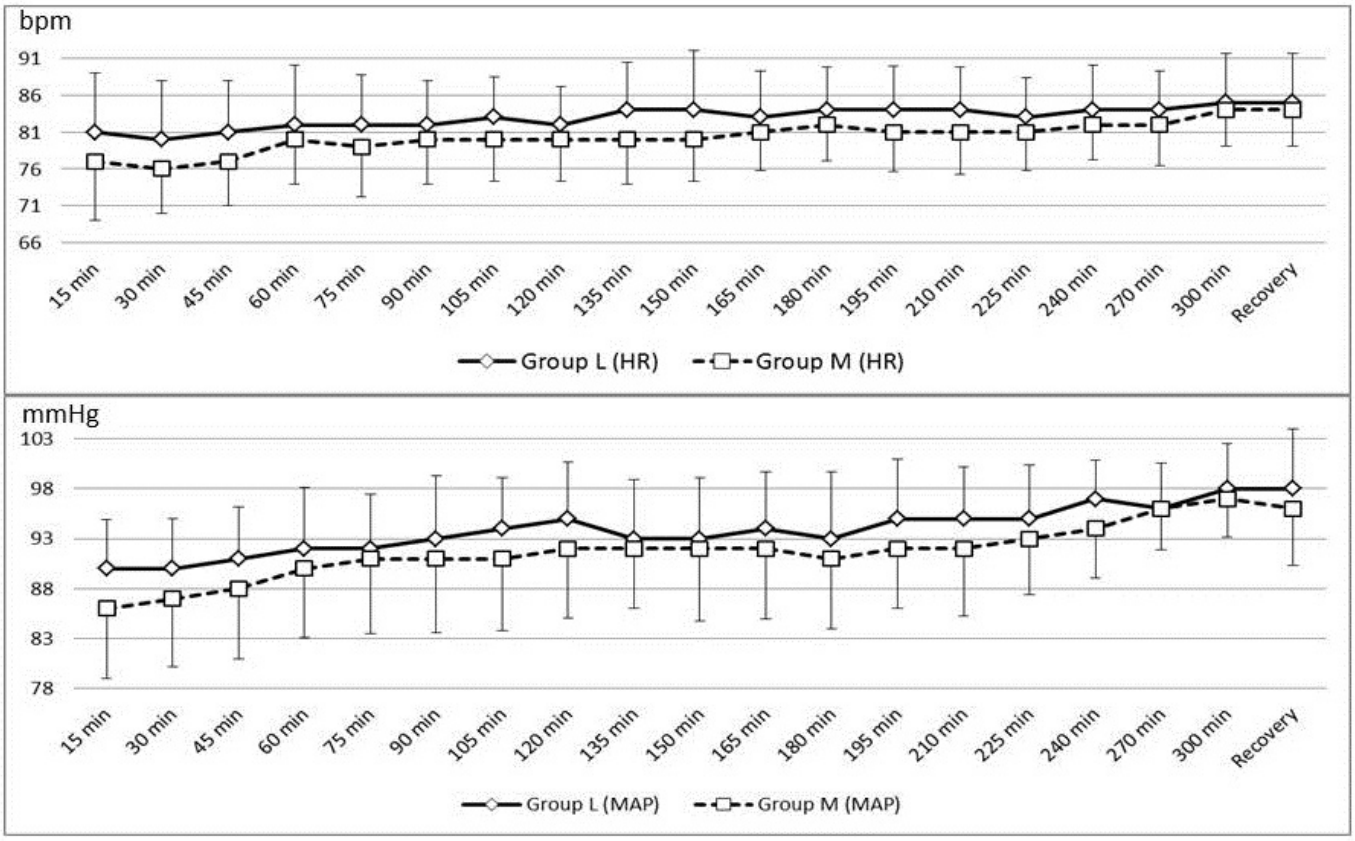


**FIGURE 2. Perioperative hemodynamic data of the included patients.**

used isoflurane concentration is plotted in Fig. 3. The BIS was comparable in the two study groups at all the time points, while the used isoflurane concentration was statistically lower at the matching time points.

Postoperative data are illustrated in Table 2. Time required for recovery was statistically shorter in group M than in group L (5.0 ± 1.0 min vs 9.8 ± 1.9 min respectively, $p = 0.00$).

The visual analogue scale was statistically lower in group M than group L at the first four hours after surgery. Concurrently, RASS was assessed after recovery was significantly different between the two groups; the greater number of patients were restless in group L than in group M.

## 5. Discussion

In this study, 50 patients undergoing elective supratentorial brain tumor surgery were randomly divided between two equal groups receiving either lidocaine infusion or magnesium sul-

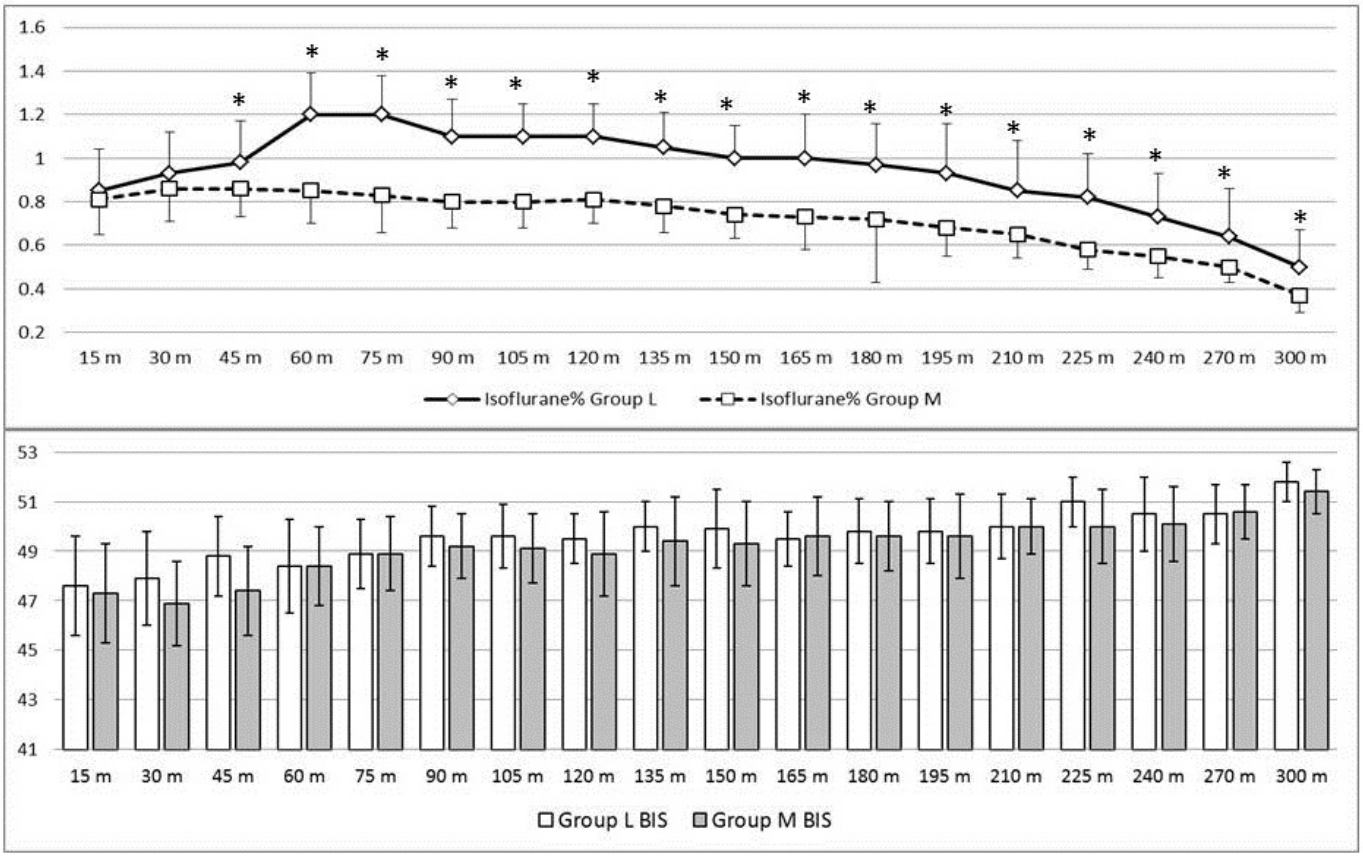


**FIGURE 3. Isoflurane concentration and BIS measurement of the included patients.**

**TABLE 2. Postoperative data for the study groups. Data are presented as mean ± SD or numbers (percentage).**

| | Group L | Group M | *p* |
|---|---|---|---|
| Recovery time (min) | 9.8 ± 1.8 | 5.1 ± 0.99 | 0.00* |
| VAS 0 | 2.7 ± 0.67 | 2.1 ± 0.33 | 0.00* |
| VAS 1 h | 3.2 ± 0.52 | 2.7 ± 0.54 | 0.001* |
| VAS 2 h | 3.6 ± 0.55 | 3.2 ± 0.73 | 0.036* |
| VAS 4 h | 2.9 ± 0.27 | 2.7 ± 0.48 | 0.034* |
| VAS 6 h | 2.2 ± 0.4 | 2 ± 0.27 | 0.23 |
| RASS | | | |
| Calm | 18 (72%) | 18 (72%) | |
| Drowsy | 1 (4%) | 5 (20%) | 0.03* |
| Restless | 6 (24%) | 2 (8%) | |

*VAS, visual analogue scale; RASS, Richmond agitation sedation scale.*
**p-value is significant if less than 0.05.*

fate infusion. Intravenous magnesium sulfate resulted in a significant decrease in the intraoperative isoflurane concentration, required muscle relaxant, also significantly decreased the recovery time, postoperative VAS score.

Essentially, anesthesia for neurosurgery aims to provide optimal surgical conditions while maintaining cerebral perfusion [1, 3]. Many adjuvants were used to assure smooth induction, intraoperative hemodynamic stability and smooth recovery, including $MgSO_4$, lidocaine and dexmedetomidine [2, 9]. Studies of perioperative magnesium infusion and lidocaine infusion investigated the analgesic effect, muscle relaxant effect, hemodynamic stabilization, and organ protective effects of both drugs [8, 10–15]. Despite magnesium sulfate and lidocaine infusion were investigated independently during neuro-anesthesia, few results can be obtained from literature comparing both agents in the same study.

Perioperative actions of magnesium sulfate are usually attributed to NMDA receptor antagonism and calcium-channel blocking activity. Many studies have examined the effects of perioperative systemic magnesium sulfate regarding its analgesic action, muscle relaxation, sedative effect and anesthesia agent saving [7, 16].

In this study, compared to lidocaine infusion, isoflurane concentration used to reach the target depth of anesthesia guided by BIS was statistically lower (M) than group (L). The postulated mechanisms for reducing anesthetic agent consumption during $MgSO_4$ infusion include reducing the sympathetic outflow and potentiation of anesthetic and hypnotic action through NMDA receptor blocking activity. Results, similar to our findings, were concluded in other studies using $MgSO_4$ infusion during total intravenous anesthesia (TIVA), where the decrease in systemic vascular resistance (SVR) and MAP lead to decreased rates of propofol, opioid infusions [11, 17, 18]. Also, the infusion of $MgSO_4$ resulted in a reduction of inhalational anesthetic consumption in laparoscopic surgery [19]. In our study, the decrease in anesthetic requirements started to show a statistical difference 45 mins after anesthesia induction, as illustrated in Fig. 3. This can be attributed to the

effect of intubation, maximum surgical stress at the beginning of the surgery, and the time required for the infused drug to reach therapeutic levels.

Concurrently, perioperative magnesium infusion in our study resulted in a significant reduction in the muscle relaxant requirement. $MgSO_4$ decreases the end-plate sensitivity and excitability through the competition with Ca+2 ions at the presynaptic terminals, enhancing the muscle relaxant action [10, 17, 20]. This effect is shown in previous studies [10, 11]. In a meta-analysis about the interaction between magnesium sulfate infusion and muscle relaxants, the infusion resulted in shorter onset time, prolonged effect and longer time for recovery from muscle relaxant effect [10].

In our study, the decreased anesthetic consumption and optimized anesthetic conditions with lower muscle relaxant doses resulted in a better recovery profile in group M. This is concordant to the results of many studies in spine surgery [13], breast surgery [21], and gynecologic surgery [22]. Similarly, Manaa and Alhabib found that $MgSO_4$ infusion in neurosurgical patients significantly reduced the recovery time from $9.8 \pm 0.9$ mins in the control group to $6.8 \pm 0.6$ mins [12].

In our results, $MgSO_4$ infusion resulted in lower postoperative VAS scores. The anti-nociceptive mechanism of $MgSO_4$ is related to both peripheral and central properties, inhibition of calcium influx and attenuation of central sensitization after peripheral tissue injury [6].

In contrast to $MgSO_4$ widely used in neuro-anesthesia, studies of lidocaine infusion in brain surgery are scarce, despite being included in many enhanced recovery protocols in non-neurosurgical settings [23]. Intraoperative infusion of lidocaine 1 $mg.kg^{-1}.h^{-1}$ for two hours improved GCS and was associated with lower inflammatory markers (IL6, PLA2) [24]. Lidocaine infusion resulted in lower VAS scores in the PACU after supratentorial tumor surgery in the study of Peng *et al.* [25]. However, the same study could not provide evidence of any improvement in neuropsychological outcome. The potential of lidocaine infusion to induce local anesthetic systemic toxicity may be the cause of regional blocks' preference than systemic administration in craniotomy.

Comparison between lidocaine and $MgSO_4$ in craniotomy is published in a preliminary study by Mahajan *et al.* [12]. In this study, pain scores and analgesic consumption in lidocaine and Mg infusion groups were comparable, and both were significantly lower than the control group. The magnesium group demonstrated a significant decrease in S100B level compared to the lidocaine group, indicating its neuroprotective effect.

The neuroprotective properties add to the value of $MgSO_4$ infusion in our study. Magnesium sulfate plays its neuroprotective role by inhibiting glutamate release, NMDA blocking action and augmentation of blood flow to cerebral ischemic regions by vascular smooth muscle relaxation. This is demonstrated in many clinical studies in head injury and brain surgeries. Also, magnesium sulfate supplementation lowered the serum level of brain injury biomarkers, S100B and Neuron-specific enolase (NSE) [12, 14, 26].

Kim MH *et al.* [27] compared both studied drugs in females undergone thyroidectomy as regarding recovery by QoR-40 scores. They found that lidocaine infusion provided better recovery scores on the first postoperative day. This results conflicts with our results, but different pathology, type and duration of surgery, doses of infused drugs and sex selection in their study may explain the cause. Also, depending on the QoR-40 scores, which may vary according to surgery's invasiveness.

Regarding the safety of the study's selected dosing regimen, Telci *et al.* [11] used a loading dose of 30 mg/kg $MgSO_4$, identical to the dose used in our study, and reported no related complications during the infusion period. Ryu *et al.* [22] reported no complications related to the loading of 50 mg/kg $MgSO_4$ in his study, where he used a larger dose than that used in ours (50 mg/kg vs 30 mg/kg). Likewise, similar to our loading dose, in the study of Groudine *et al.* [28], the loading of lidocaine 1.5 mg/kg in is expected to give a plasma concentration (1.3–3.7 $\mu$/mL) that is far from levels (5 $\mu$/mL) required for toxicity, where none of the included patients showed related complications and one patient was excluded due to surgical issues. Also, the safety of perioperative loading and infusion of lidocaine is established by a systemic review of sixteen randomized trials in different anesthetic fields [29]. As mentioned in the results, none of the patients showed side effects related to the study medication.

This study has some limitations. We did not measure serum levels of lidocaine and $MgSO_4$. However, the used doses were previously used in many studies supporting the safety of the study protocol. The relatively small study group and short follow up period is another limitation. Larger and multi-centre studies with a longer follow up period are recommended. A focused assessment of the effects of the study drugs on stress response to specific surgical events like intubation, skin incision, pin-head holder insertion is warranted.

In conclusion, compared to lidocaine infusion, $MgSO_4$ infusion resulted in lower anesthetic drugs consumption, muscle relaxant requirement, a shorter recovery time, and a better postoperative pain profile. $MgSO_4$ can be used effectively as an adjuvant during anesthesia for brain surgery with superior clinical properties than lidocaine infusion.

## AUTHOR CONTRIBUTIONS

MAA: the author prepared the study design, participate in data collection, writing the manuscript, and submission. AKA: the author participates in data collection, reviewing the manuscript, and did statistical analysis.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethical committee of Mansoura faculty of medicine in the form of the institutional research board (IRB #R 20.06.913, July 5-2020), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrolment at the Pan African Clinical Trial Registry system (PACTR 202007774954789, July 17-2020).

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. Mohamed Adel Aboelela is a Guest Editor of this journal.

## DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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