Magnesium sulphate has beneficial effects as an adjuvant during general anaesthesia for Caesarean section

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Background. The use of low concentrations of volatile anaesthetics with avoidance of opioids may induce intraoperative awareness and adverse haemodynamic responses during Caesarean section. Magnesium is well known to reduce anaesthetic requirements and to block noxious stimuli. We investigated whether i.v. magnesium sulphate modulates anaesthetic depth and analgesic efficacy during Caesarean section.

Methods. Seventy-two patients undergoing Caesarean section were randomly assigned to receive i.v. saline (control group) or magnesium sulphate 30 mg kg\(^{-1}\) bolus + 10 mg kg\(^{-1}\) h\(^{-1}\) continuous infusion (Mg 30 group) or 45 mg kg\(^{-1}\) bolus + 15 mg kg\(^{-1}\) h\(^{-1}\) continuous infusion (Mg 45 group) after induction. Bispectral index (BIS) value, mean arterial pressure (MAP), and midazolam, fentanyl, and atracurium consumptions were recorded.

Results. BIS values [mean (SD)] at 7.5 and 10 min after surgery and before delivery in the control [64 (9), 66 (8), 67 (8), \(P<0.001\)] and the Mg 30 groups [62 (8), \(P<0.01\); 64 (7), 63 (9), \(P<0.001\)] were higher than in the Mg 45 group [56 (8), 55 (8), 55 (7)]. MAP was greater in the control group (\(P<0.05\)) than in the Mg 30 and Mg 45 groups during the pre-delivery period. The magnesium groups required less midazolam (\(P<0.05\)), fentanyl (Mg 30, \(P<0.05\); Mg 45, \(P<0.01\)), and atracurium (\(P<0.001\)) vs the control group.

Conclusions. Preoperative i.v. magnesium sulphate attenuated BIS and arterial pressure increases during the pre-delivery period. Magnesium sulphate can be recommended as an adjuvant during general anaesthesia for Caesarean section to avoid perioperative awareness and pressor response resulting from inadequate anaesthesia, analgesia, or both.

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Low concentrations of volatile anaesthetic agents and the avoidance of opioids until delivery have traditionally been used for Caesarean section, because of concerns regarding uterine atony and neonatal respiratory depression. As a result, pregnant women undergoing general anaesthesia for Caesarean section have a higher incidence of intraoperative awareness than general surgical patients, especially during the period before neonatal delivery.\(^1\)\(^2\) A previous study demonstrated that the use of sevoflurane 1% in N\(_2\)O 50% without analgesics failed to maintain bispectral index (BIS) levels consistent with unconsciousness during Caesarean section.\(^3\) Furthermore, adverse haemodynamic stress responses such as severe increases in arterial pressure due to inadequate anaesthesia, analgesia, or both during the pre-delivery period can be a risk factor in obstetric patients with pre-existing essential hypertension, ischaemic cardiac disease, or increased intracranial or intraocular pressure.

Magnesium sulphate has been widely used as a tocolytic agent and an anticonvulsant for the treatment of preterm labour and pre-eclampsia, respectively. On the other hand, perioperative magnesium sulphate has been reported to reduce anaesthetic requirements\(^4\)\(^5\)\(^6\) and to shorten anaesthetic induction by propofol.\(^4\)\(^6\)\(^7\) Moreover, in these
studies, the time required to reach a BIS value of 60 was significantly less for magnesium-treated patients than untreated controls. In addition, magnesium has also been reported to have antinociceptive effects in animal and human models of pain, and to reduce intraoperative analgesic consumption.

We therefore hypothesized that the anaesthetic and analgesic potency of magnesium sulphate might be beneficial in terms of attenuation of BIS increase and maintaining stable haemodynamics via blockade of painful stimuli before neonatal delivery. To our knowledge, no other study has been conducted on the role of magnesium sulphate as an anaesthetic adjuvant during Caesarean section. In this study, we investigated the ability of magnesium sulphate to modulate anaesthetic depth and analgesic efficacy in patients undergoing general anaesthesia for Caesarean section.

Methods

After obtaining institutional review board approval and informed consent, 75 ASA physical status I subjects undergoing elective Caesarean section under general anaesthesia were enrolled in this study. The indications for Caesarean section were breech presentation, cephalopelvic disproportion, or previous Caesarean delivery. Patients with the following conditions were excluded from the study: hypermagnesaemia, a known hypersensitivity to magnesium sulphate, any degree of heart block, hypertension, diabetes mellitus, cardiovascular, or kidney disease, labour pain requiring analgesics, preterm, multiple gestation, preoperative fetal distress, or any other medical complication.

The subjects were randomly divided into one of the three groups by using a computer-generated random number table: the Mg 30 group (n=25) received magnesium sulphate 10% (30 mg kg⁻¹) as an i.v. bolus and 10 mg kg⁻¹ h⁻¹ by a continuous infusion, the Mg 45 group (n=25) received magnesium sulphate 10% (45 mg kg⁻¹) as a bolus and 15 mg kg⁻¹ h⁻¹ by a continuous infusion, and the control group (n=25) received a similar volume of saline as bolus and continuous infusion. Each study drug was prepared by the anaesthesiologist responsible for subject grouping.

Before the induction of anaesthesia, standard monitoring devices (Multi Channel Anaesthesia Monitor S/5TM, Datex-Ohmeda, Beaverton, OR, USA) were applied. A BIS A-2000 monitor (Aspect Medical Systems, Newton, MA, USA) was used to continuously measure and display BIS values. Muscle relaxation was monitored using a neuromuscular monitor (TOF-Watch®, Organon, Dublin, Ireland) with two electrodes attached on the ulnar side of the wrist.

After obtaining baseline values for BIS and haemodynamic variables, anaesthetic induction was performed using thiopental sodium 4 mg kg⁻¹, followed by the bolus study drug given over 15–20 s, and then succinylcholine 1–1.5 mg kg⁻¹, followed by the study drug given by continuous infusion by an attending anaesthesiologist who was blinded to the grouping and study drug. Cricoid pressure was applied and the trachea was intubated 90 s after administration of the succinylcholine. Atracurium 0.25 mg kg⁻¹ was administered for further muscle relaxation.

Anaesthesia was maintained with 1.0% end-tidal sevoflurane and 1:1 O₂/N₂O at 3 litre min⁻¹. Ventilation of the lungs was adjusted to maintain an end-tidal carbon dioxide of 4.4–4.7 kPa. BIS values were recorded at 2.5 min intervals from induction of anaesthesia to delivery. Mean arterial pressure (MAP) and heart rates were measured before the induction of anaesthesia; just after intubation; at 5 and 10 min after surgery; and before delivery. After delivery, midazolam or fentanyl was administered, as required, to achieve adequate sedation or analgesia to the end of surgery. The target BIS range was 40–60. If BIS values exceeded 60 for more than 10 s, midazolam 0.05 mg kg⁻¹ was administered. Inadequate analgesia was defined as a condition during which MAP or heart rate increased by 20% vs baseline and required fentanyl 1.0 µg kg⁻¹ for management. Train-of-four (TOF) supramaximal neuromuscular stimulation (2 Hz, 50 mA) was measured at 5 min intervals to the end of surgery and at 1 min intervals thereafter. Atracurium (0.1 mg kg⁻¹) was injected when a TOF count exceeded two until 10 min before the end of surgery. The total amounts of midazolam, fentanyl, and atracurium administered after delivery were recorded, and divided by subject’s body weight and surgery time (results are presented in µg kg⁻¹ h⁻¹). Times from induction to skin incision, times from uterine incision to delivery, times from induction to delivery, neonatal Apgar scores, and estimated blood losses were also recorded.

Sevoflurane and N₂O administration were immediately discontinued after skin closure, and subjects were then ventilated with O₂ 100% at 5 litre min⁻¹. Subjects were allowed to recover spontaneously until the return of T1=25% or >2 responses on neuromuscular monitoring. Then glycopyrrolate and pyridostigmine were administered i.v. to reverse muscle relaxation. Tracheal tubes were removed when BIS reached 80 and TOF ratio (T4/T1) was >0.7. Times required to return to a T1 of 25%, to respond to verbal commands (spontaneous eye opening), and to tracheal extubation were recorded. All data were recorded by an anaesthesiologist unaware of the study protocol and study drugs used. Subjects were interviewed regarding intraoperative recall on discharge from the postoperative care unit.

The primary outcome variable of the study was difference in the BIS value. On the basis of our pilot study, a prior power analysis indicated that a minimum of 21 subjects per group would be sufficient to detect a 10% difference in BIS values among the groups after the administration of magnesium sulphate, with a study power of 80% (β=0.20) and a sensitivity of 95% (α=0.05). Intra-group differences were analysed by two-way repeated-measures analysis of variance (ANOVA) with
Tukey’s post hoc test. Inter-group differences were compared using one-way ANOVA with Scheffe’s post hoc test among the groups. P-values of <0.05 were considered significant. Statistical analysis was performed using SPSS® 17.0 software (SPSS Inc., Chicago, IL, USA). Data are expressed as mean (range or SD) or median (range).

### Results

Seventy-two subjects completed the study. Three subjects were excluded from the analysis because the pre-delivery period was <10 min (one in the Mg 30 group) or because of technical problems with the neuromuscular monitor (one in the control group and one in the Mg 30 group).

There were no differences in patient characteristic data and maternal and neonatal outcome variables among the study groups (Table 1). No neonate required resuscitation in all three study groups.

BIS changes from induction of anaesthesia to delivery are shown in Table 2. BIS values during the pre-induction period were similar in all three study groups. BIS values remained at <60 in all subjects until 2.5 min after the initiation of surgery. However, BIS values at 7.5 and 10 min after surgery, and pre-delivery in the control [61 (9), 64 (9), 66 (8), 67 (8), P<0.001] and Mg 30 groups [59 (7), P<0.05; 62 (8), 64 (7), 63 (9), P<0.001]. However, BIS values were unchanged during the pre-delivery period in the Mg 45 group vs before magnesium sulphate administration [54 (8)].

MAP and heart rates before induction were similar in the three groups (Table 3). However, MAP was significantly higher in the control group than in the Mg 30 and Mg 45 groups post-intubation [112 (15) vs 101 (12), P<0.05; 115 (15) vs 95 (11) mm Hg, P<0.001], at 5 min [104 (9) vs 89 (7), P<0.001; 104 (9) vs 85 (10) mm Hg, P<0.001] and at 10 min [102 (7) vs 87 (9), P<0.01; 102 (7) vs 84 (11) mm Hg, P<0.001] after surgery, and pre-delivery [96 (6) vs 85 (9), P<0.05; 96 (6) vs 83 (11) mm Hg, P<0.01]. When compared with pre-induction values, MAP was higher post-intubation, at 5 and 10 min after surgery, and pre-delivery in the control group (P<0.001), but was only higher post-intubation in the Mg 30 (P<0.001) and Mg 45 (P<0.001) groups. No significant difference was observed between MAP values in the magnesium-treated groups, and heart rates were similar for all groups.

Midazolam, fentanyl, and atracurium consumptions are presented in Table 4. Midazolam consumption was significantly lower in the Mg 30 [75.9 (19.7) μg kg⁻¹ h⁻¹, P<0.05] and Mg 45 groups [67.5 (18.3) μg kg⁻¹ h⁻¹, P<0.05] than in the control group [103.7 (23.1) μg kg⁻¹ h⁻¹]. Significantly lower doses of fentanyl were required by the Mg 30 [0.4 (0.3) μg kg⁻¹ h⁻¹, P<0.05] and Mg 45 groups [0.2 (0.2) μg kg⁻¹ h⁻¹, P<0.01] than by the control group [1.1 (0.4) μg kg⁻¹ h⁻¹], and atracurium doses were significantly lower in the Mg 30 [220.3 (67.8) μg kg⁻¹ h⁻¹, P<0.001] and Mg 45 groups [183.7 (78.1) μg kg⁻¹ h⁻¹, P<0.001] than in the control group [340.7 (81.7) μg kg⁻¹ h⁻¹]. No difference was observed between drug consumptions in the Mg 30 and Mg 45 groups.

Maternal recovery times were not significantly different among the groups (Table 5), and no patient experienced intraoperative recall.
The majority of studies have observed that the induction of Caesarean section. BIS values below 60 indicated a low sedation, analgesia, or both during general anaesthesia for monitoring can be a useful means of detecting inadequate sedation,11 12 and are increased by not reliably producing BIS values below 60 during the noxious stimuli, but that 45 mg kg\(^{-1}\) of magnesium sulphate as a bolus and 15 mg kg\(^{-1}\) h\(^{-1}\) by a continuous infusion effectively prevents awareness, as indicated by attenuated BIS increases during the pre-delivery period in patients under general anaesthesia for Caesarean section. The study also demonstrates that after neonatal delivery, midazolam, fentanyl, and atracurium consumptions were significantly reduced total midazolam consumption, which is the first randomized, double-blind, placebo-controlled study to investigate the effects of magnesium during Caesarean section. Our results show that the pre-operative administration of magnesium sulphate not only attenuates increases in arterial pressure resulting from noxious stimuli, but that 45 mg kg\(^{-1}\) of magnesium sulphate as a bolus and 15 mg kg\(^{-1}\) h\(^{-1}\) by a continuous infusion effectively prevents awareness, as indicated by attenuated BIS increases during the pre-delivery period in patients under general anaesthesia for Caesarean section. The study also demonstrates that after neonatal delivery, midazolam, fentanyl, and atracurium consumptions were significantly lower in the magnesium groups than in the control group.

In the present study, we used BIS monitoring and chose a BIS target range of 40–60. Because BIS levels correlate well with depth of sedation,11 12 and are increased by not only awareness13 but also sympathetic activation,14 BIS monitoring can be a useful means of detecting inadequate sedation, analgesia, or both during general anaesthesia for Caesarean section. BIS values below 60 indicated a low probability of recall and intraoperative awareness in the majority of studies.12 15 16 We observed that the induction of anaesthesia with thiopental and maintenance with 1.0% end-tidal sevoflurane in N\(_2\)O 50% in the control group did not reliably produce BIS values below 60 during the period between 5 min after surgery and delivery, which concurs with the result of previous study.3

The role of magnesium sulphate on BIS response is debatable in a few studies. In one previous study, when patients received either sufentanil infusion or sufentanil plus magnesium sulphate (2 g h\(^{-1}\) infusion), the magnesium infusion reduced sufentanil consumption but did not significantly change BIS values.17 However, in this study, average BIS values were kept in the range 61–88 by decreasing or increasing sufentanil infusion in both groups, and immediate BIS values after the administration of magnesium sulphate were not presented. In another study, the authors suggested that one of the reasons for the BIS increase observed in their study was a reduced propofol requirement resulting from the anaesthetic effect of magnesium sulphate.5 On the other hand, in another study, i.v. magnesium sulphate (30 mg kg\(^{-1}\) as a bolus dose followed by a continuous infusion of 10 mg kg\(^{-1}\) h\(^{-1}\) not only significantly reduced total midazolam consumption, but also decreased BIS values over 10 min after administration in patients under monitored anaesthesia care for shockwave lithotripsy.18 In the present study, although BIS values increased above 60 from 7.5 min after surgery in the Mg 30 group, the time required to reach a BIS value of above 60 was substantially later in the Mg 30 group compared with the control group. Moreover, in the Mg 45 group, mean BIS values remained in the target range during the entire pre-delivery period.

Recent studies have demonstrated that magnesium administration significantly reduces anaesthetic drug requirements.4–7 18 19 Similar to other studies,18 20 we also observed a significant reduction in midazolam consumption during the operation period in magnesium-treated subjects. This finding, in addition to the observed attenuations of BIS increases, suggests that magnesium sulphate may have a sedative effect and, thus, might be beneficial in patients undergoing general anaesthesia for Caesarean section who have a high risk of awareness, especially during the pre-delivery period.
Noxious stimuli, such as laryngoscopy, orotracheal intubation, and skin and uterine incisions, are frequent during the period before neonatal delivery, but despite the need for adequate analgesia during this period, opioids are usually avoided because of the risk of neonatal respiratory depression. However, no side-effect-free agent that specifically inhibits nociception during Caesarean section has yet been identified. In the present study, haemodynamic responses to noxious stimuli during the pre-delivery period were effectively blunted in the magnesium-treated groups, with no significant inter-group differences. From post-intubation to pre-delivery, MAP remained at a significantly lower level in magnesium sulphate-treated subjects than in controls; this probably indicates that the analgesic properties of magnesium sulphate reduce sympathetic stimulation. Furthermore, mean intraoperative fentanyl consumptions in the Mg 30 and Mg 45 groups were significantly less than in the control group. This finding is in accord with previous studies, which found that the use of magnesium sulphate as an adjuvant reduces analgesic requirements during the perioperative period under general anaesthesia.6 9 10

Magnesium is a physiologic calcium channel blocker21 and a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist,22 and these properties appear to play an important role in the prevention and treatment of perioperative pain.23 24 Furthermore, the potency of volatile anaesthetics can be increased by non-competitive NMDA antagonist, and the analgesic effects of magnesium are probably enhanced by volatile anaesthetics.25 Taken together, we suggest that antagonism of NMDA receptor and blockade of calcium channel by magnesium could be responsible for the modification of perioperative sedation and analgesia observed in the present study. On the other hand, magnesium blocks the release of catecholamines26 27 and produces vasodilatation by acting directly on blood vessels,28 and thus, we cannot exclude the possibility that those effects could have partly contributed to the improved arterial pressure control observed in the Mg 30 and Mg 45 groups. However, obviously further studies are needed to identify the precise mechanism.

It is well known that magnesium sulphate prolongs and potentiates neuromuscular block by non-depolarizing neuromuscular blocking agents,29 and our results support previous clinical studies3 10 by demonstrating that magnesium lowers neuromuscular blocker requirements. In a previous study, magnesium sulphate was found to delay postoperative recovery.7 However, in the present study, maternal emergence and recovery were virtually identical in the three groups, probably because neuromuscular transmission was monitored throughout the operation, additional doses of atracurium were administered according to the TOF count >2 criterion, atracurium injections were discontinued from 10 min before the end of surgery, and atracurium consumptions were lower in the magnesium-treated groups than in the control group.

One limitation is that serum magnesium concentrations were not measured in our study. However, the doses of magnesium sulphate used in the present study were lower than those used to treat pre-eclampsia, which requires a loading dose of magnesium sulphate 4 g, followed by 1–2 g h⁻¹ as a maintenance dose,30 and were within the ranges used in previous investigations.4 6 19 31 In addition, previous studies, in which similar magnesium regimen was used, had noted almost 1.4–1.8 times increase in serum magnesium concentrations.5 9 32 No increase in blood loss or uterine atony occurred, and no adverse neonatal effects were observed at the dosages used in the present study.

In conclusion, our results show that the preoperative administration of magnesium sulphate reduced intraoperative requirements for midazolam, fentanyl, and atracurium. Furthermore, magnesium sulphate effectively attenuated BIS and arterial pressure increases during the period before neonatal delivery. Our findings indicate that magnesium sulphate can be recommended as an adjuvant during general anaesthesia for Caesarean section, to avoid perioperative awareness and pressor response resulting from inadequate anaesthesia, analgesia, or both.

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References
3 Chin KJ, Yeo SW. Bispectral index values at sevoflurane concentrations of 1% and 1.5% in lower segment cesarean delivery. Anesth Analg 2004; 98: 1140–4
5 Choi JC, Yoon KB, Um D, Kim C, Kim JS, Lee SG. Intravenous magnesium sulfate administration reduces propofol infusion requirements during maintenance of propofol–N₂O anesthesia: part I: comparing propofol requirements according to hemodynamic responses: part II: comparing bispectral index in control and magnesium groups. Anesthesiology 2002; 97: 1137–41
8 McCarthy RJ, Krown JS, Tuman KJ, Penn RD, Ivankovich AD. Antinociceptive potentiation and attenuation of tolerance by
23 Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991; 44: 293–9
32 Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology 2001; 95: 640–6