



CLINICAL RESEARCH

Intravenous magnesium sulfate for postoperative analgesia after abdominal hysterectomy under spinal anesthesia: a randomized, double-blind trial

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Abstract

Background and objectives: Abdominal Hysterectomy (AH) is associated with significant inflammatory response and can result in moderate to severe postoperative pain. This study aimed to evaluate the efficacy of magnesium infusion in reducing postoperative pain and analgesic consumption after AH under spinal anesthesia with Intrathecal Morphine (ITM).

Method: Eighty-six patients were included in this clinical, controlled, randomized, double-blind study. Patients received in Group Mg, MgSO_4 50 mg kg^{-1} for 15 minutes followed by $15 \text{ mg kg}^{-1} \text{ h}^{-1}$ until the end of the surgery; and in Group C, (control) the same volume of isotonic saline. Both groups received $100 \mu\text{g}$ of ITM. All patients received dipyrone + ketoprofen intraoperatively and postoperatively, and dexamethasone intraoperatively only. We evaluated the intensity of pain, tramadol consumption, and adverse events 24 hours postoperatively.

Results: Serum magnesium concentrations were higher in Group Mg at the end, and one hour after the operation ($p = 0.000$). Postoperative pain scores were reduced in Group Mg at 6 hours at rest and on movement ($p < 0.05$). Tramadol consumption did not show a statistically significant difference between Group Mg and Group C ($15.5 \pm 36.6 \text{ mg}$ and $29.2 \pm 67.8 \text{ mg}$ respectively, $p = 0.53$). Hemodynamic variables, the incidence of pruritus, nausea, and vomiting were similar in the two groups.

Conclusion: Infusion of MgSO_4 during AH undergoing spinal anesthesia with ITM reduced at 6 hours at rest and on movement. More studies should be performed to evaluate the potential antinociceptive effect of MgSO_4 in scenarios where a multimodal analgesia approach was employed.

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Introduction

Hysterectomy is the most common major gynecologic operation and is usually performed through laparotomy.¹ Abdominal Hysterectomy (AH) is associated with an intense inflammatory response that can result in moderate to severe postoperative pain, sometimes difficult to control.^{2,3} Adequate analgesia that allows early mobilization with fewer complications is essential for improved postoperative recovery.^{4,5} Perioperative regional anesthesia is often used in fast-track programs. Spinal anesthesia with intrathecally applied opioids may further optimize postoperative pain management after AH.^{6,7} The most commonly used doses of morphine range from 100 to 200 μg , with higher doses increasing the adverse effects, especially nausea, vomiting, and postoperative itching.^{7,8} To minimize these adverse effects and optimize analgesia, it has been attempted to associate adjuvants.^{9,10} Intravenous (IV) magnesium is used as an adjuvant due to its analgesic properties. Although the exact mechanism is not fully understood, the analgesic properties of magnesium are based on acting as a non-competitive antagonist of N-Methyl-D-Aspartate (NMDA) receptors in central nervous system and regulating the calcium influx into the cell. These properties avoid the central sensitization mechanisms due to the stimulation of peripheral nociceptive nerves.¹¹ To our knowledge, no previous studies have addressed the use intravenous (IV) of magnesium in patients undergoing hysterectomy under spinal anesthesia with Intrathecal Morphine (ITM), which may be a more efficacious alternative for the postoperative analgesia. Therefore, we conducted this study to evaluate the efficacy of the magnesium to the analgesia after abdominal hysterectomy under spinal anesthesia with ITM.

Methods

The Research Ethics Committee of the institution approved this study. This trial was registered in the Brazilian Clinical Trials database (RBR-7B5X5K). We obtained written, informed consent from all patients. Between October 2016 and December 2018, patients aged between 18 and 65 years, ASA (American Society of Anesthesiologists) physical status I to III and scheduled to undergo abdominal hysterectomy were eligible to participate in this prospective, randomized, controlled, double-blind study. Exclusion criteria included Body Mass Index (BMI) $\geq 40 \text{ kg m}^{-2}$, previous abdominal surgery (except cesarean delivery), oncological surgery, severe cardiovascular, renal, and hepatic dysfunction, neuromuscular diseases, using calcium channel blockers, and inappropriate for spinal anesthesia.

Randomization lists were computer-generated. During preparation for surgery, a nurse, educated on how to prepare the drugs, opened the sealed black envelopes containing the groups, and prepared the infusions. In this manner, patients were randomized to receive one of two regimens: in the Group Mg, IV Magnesium Sulfate (MgSO_4) 50 mg kg^{-1} (regarding the ideal body weight) in 100 mL of isotonic saline over 15 minutes immediately before spinal anesthesia, and then 15 $\text{mg kg}^{-1} \text{ h}^{-1}$ until the end of the operation (MgSO_4 at a concentration of 100 mg mL^{-1}); in the Group C (control), the same volume of isotonic saline over

the same period. For example, a patient weighing 80 kg received 40 mL of the solution in 15 minutes, followed by 12 mL h^{-1} of the same solution until the end of the operation, either in the intervention group or in the control group. Patients, anesthesiologists, and surgeons were unaware of the randomization process or the types of infusion used. An observer who was blinded to both groups recorded the study data.

Anesthesia and operative techniques

The patients had nothing by mouth overnight. In the operation room, routine monitorization including electrocardiography, pulse oximetry, and noninvasive blood pressure were implemented. Then, an 18G IV cannula was inserted. Oxygen 3–4 L min^{-1} was administered via a nasal catheter. Then, each patient received boluses of 0.03 mg kg^{-1} of midazolam and 0.25 $\mu\text{g kg}^{-1}$ of fentanyl for sedation, aiming to a Ramsay Sedation Scale score of 3.¹² Before anesthesia onset, all patients received 500 mL of Ringer's lactate solution and 10 $\text{mL kg}^{-1} \text{ h}^{-1}$ of the same solution until the end of the operation. An anesthesiologist performed spinal anesthesia through L3–4 or L4–5 interspace in lateral decubitus position and using 25G or 27G Quincke needles. After confirming the cerebrospinal fluid flow, 3.5 mL of 0.5% hyperbaric bupivacaine +100 μg of morphine was administered over 30 seconds. Immediately after the blockade, patients were placed in horizontal dorsal decubitus. The loss of pinprick sensation evaluated the level of sensory block. The start of the operation was authorized as soon as the T6 dermatome was reached. In operation, the Pfannenstiel incision was used. Hypotension was defined as a decrease in systolic arterial blood pressure by 20% from baseline values, and it was treated with ephedrine 5 mg IV. Bradycardia was defined as heart rate decreases to less than 50 bpm, and it was treated with atropine 0.5 mg IV. All the patients received cefazolin 2 g, dexamethasone 10 mg, ketoprofen 100 mg, and dipyron 2 g IV at the beginning of the surgery and ondansetron 4 mg IV at the end of surgery. Ketoprofen 100 mg and dipyron 2 g IV were maintained every 6 and 8 hours after surgery, respectively. Pain scores were evaluated using a 0–10 cm visual analog scale (VAS, from 0, no pain, to 10, worst pain imaginable). In the Post-Anesthesia Care Unit (PACU) and after discharge to the ward (discharge readiness from the PACU was assessed by using the modified Aldrete's score¹³ every 15 minutes until patients met discharge criteria (score = 10), tramadol 100 mg IV was administered when VAS scores were > 3, or the patient requested analgesic. Nausea and Vomiting (NVPO) were treated with 4 mg ondansetron intravenously.

Outcome variables

The primary outcomes of this study were the pain intensity assessed at rest and on movement (from lying to sitting on the bed) at 6 and 24 hours after the operation, using the VAS score. Secondary endpoints included the tramadol consumption and occurrence of hypotension, bradycardia, NVPO, and pruritus 24 hours postoperatively. Demographic variables, ASA physical status, previous cesarean delivery, comorbidities, and duration of surgery were recorded for

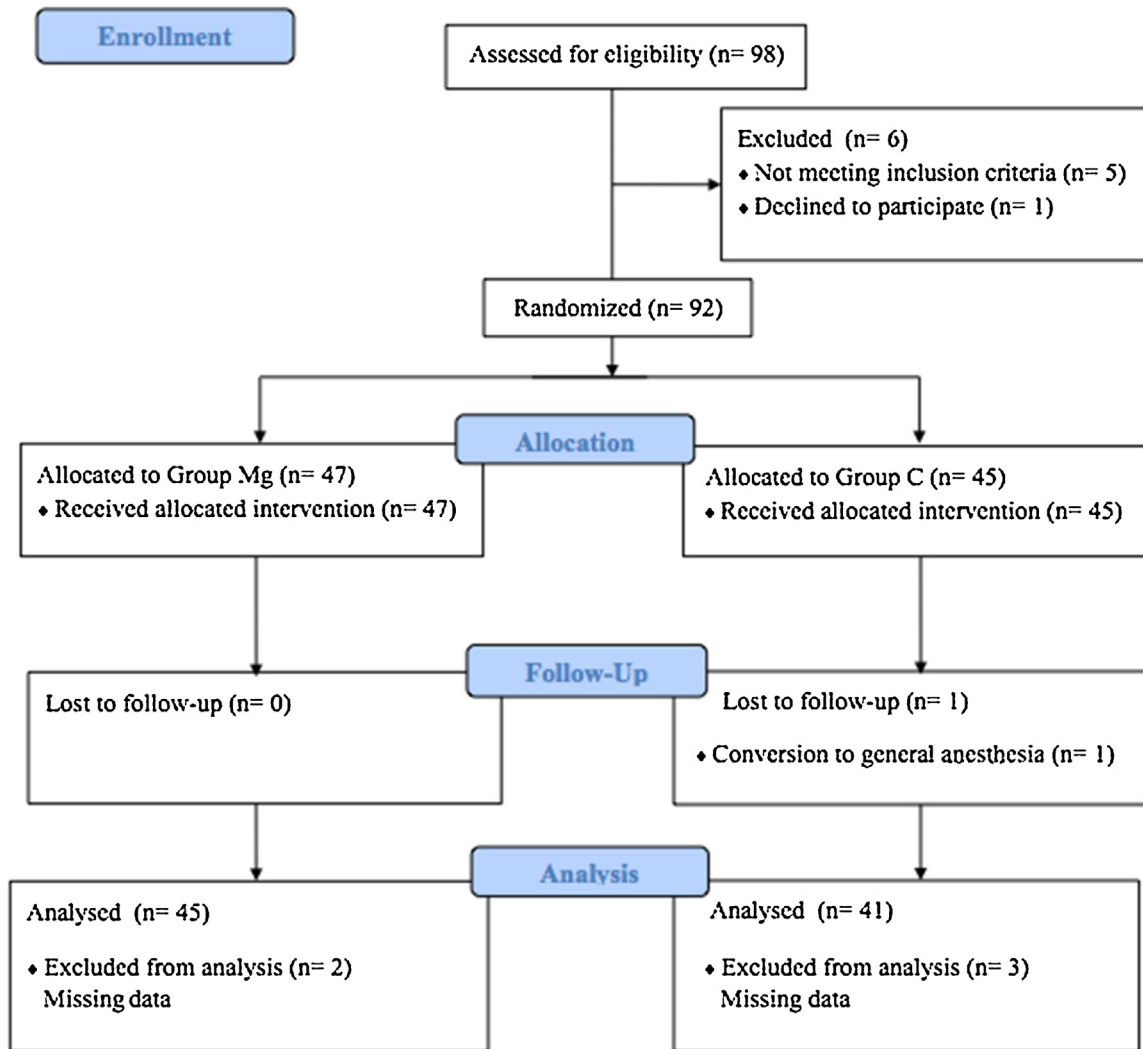


Figure 1 The flow chart of the study.

each patient. Hemodynamic variables: Mean Arterial Blood Pressures (MAP) and Heart Rates (HR) were recorded at time 0 (before the study drug infusion), 15, 30, 60, 90, and 120 minutes during the surgery, and one hour after admission in the PACU. The serum level of magnesium was assessed immediately before, in the end, and one hour after the operation.

Statistical analysis

The sample size calculation was based on the mean \pm Standard Deviation (SD) 4.2 cm (1.9) pain scores on movement from a pilot study involving hysterectomies under spinal anesthesia. We considered a reduction in the mean intensity pain score of 1.26 cm as clinically significant. A sample size, taking into consideration an α error of 5% and a β error of 20%, was calculated as at least 36 patients per group. Continuous data with normal distribution were analyzed by the Student's *t* test for independent samples. Continuous data without normal distribution or discrete data were analyzed using the Mann-Whitney test. For cate-

gorical data, the Chi-Square test or Fisher's exact test was used. Generalized estimating equations model was used for comparative analysis of the evolution of the variables MAP and HR over time between groups. A significant difference was set at p -value < 0.05 . For the statistical analysis, SPSS version 21.0 was used.

Results

Ninety-eight patients were recruited for the study. Ninety-two patients were randomized to the study. One patient was excluded due to conversion to general anesthesia. Five patients were excluded due to missing data. The data of 86 patients were analyzed. The flow diagram of recruitment, allocation, follow-up, patient analysis, and causes of exclusion is shown in [Figure 1](#).

There were no significant differences between groups regarding patient demographics, ASA physical status, comorbidities, the occurrence of previous cesarean delivery, and duration of surgery ([Table 1](#)).

Table 1 Baseline characteristics of the patients in the groups.

	Group Mg (n = 45)	Group C (n = 41)	p-value
Age (years) ^a	44.5 ± 6.7	45.9 ± 7.7	0.39
Weight (Kg) ^a	70.0 ± 12.8	73.0 ± 13.8	0.29
Height (cm) ^a	161.3 ± 5.6	162.0 ± 6.7	0.59
ASA (I/II/III) ^b	20/24/1	18/22/1	0.99
Previous CD (Yes/No) ^b	22/23	27/14	0.16
Duration of surgery ^b	107.4 ± 28.8	103.9 ± 28.5	0.57
Comorbidities ^b			
SAH (n, %)	13 (28.8)	12 (29.2)	0.92
DM (n, %)	3 (6.6)	2 (4.8)	
Other (n, %)	6 (13.3)	4 (9.6)	

Values are mean ± standard deviation, n or n (%). ASA, American Society of Anesthesiologists physical Status; CD, Cesarean Delivery; SAH, Systemic Arterial Hypertension; DM, Diabetes Mellitus.

^a Student's *t* test.

^b Chi-square test.

Table 2 Serum magnesium concentration (mEq.L⁻¹) in the study groups.

	Group Mg (n = 45)	Group C (n = 41)	p-value
Preoperative	2.0 (0.9–3.0)	1.8 (0.8–2.7)	0.63
Immediately after operation	3.1 (1.5–4.8)	1.9 (0.9–2.8)	0.000
One hour after operation	3.2 (1.7–4.2)	1.9 (0.9–2.8)	0.000

Values are mean (minimum – maximum). Student's *t* test.

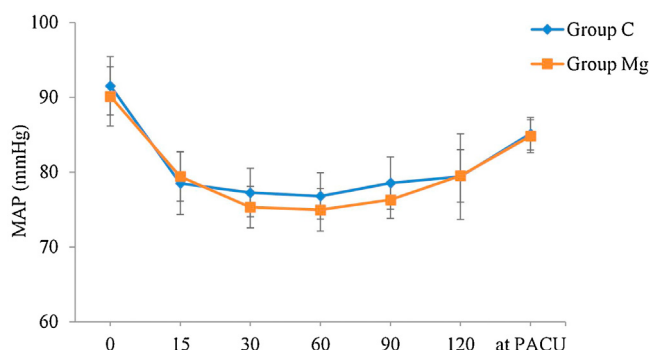


Figure 2 Mean arterial pressure (mean and 95% confidence interval) according to group and time. Horizontal axis: 0 (baseline), 15, 30, 60, 90, 120 minutes, and at Postanesthesia Care Unit (PACU). Variable group ($p=0.59$); variable time ($p=0.000$); variable time versus group ($p=0.73$). Generalized estimating equations model.

Postoperative serum magnesium concentrations in Group Mg were significantly higher than those in Group C immediately after surgery, and at one hour after surgery ($p=0.000$) (Table 2).

MAP was similar in the two groups ($p=0.59$). There was no interaction between group and time ($p=0.73$), but there was a decrease in MAP over time (baseline > 15, 30, 60, 90 minutes, and at PACU) with progressive recovery at the end of the observed period (at PACU > 30, 60, and 120 minutes), $p=0.000$ (Figure 2).

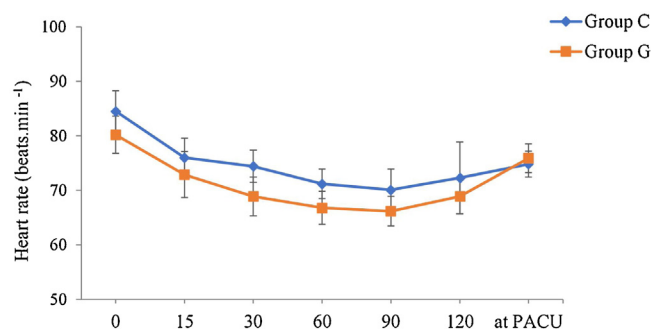


Figure 3 Heart rate (mean and 95% Confidence Interval) according to group and time. Horizontal axis: 0 (baseline), 15, 30, 60, 90, 120 minutes, and at Postanesthesia Care Unit (PACU). Variable group ($p=0.054$); variable time ($p=0.000$); variable time versus group ($p=0.12$). Generalized estimating equations model.

Mean HR was similar in the two groups ($p=0.054$). There was also no interaction between group and time ($p=0.12$), but there was a decrease in HR over time (baseline > 15, 30, 60, 90 minutes, and at PACU) with progressive recovery at the end of the observed period (at PACU > 30, 60, and 90 minutes), $p=0.000$ (Fig. 3).

The incidence of hypotension was similar between the two groups: Group Mg, 31.1%, and Group C, 17.1%, ($p=0.14$). The incidence of bradycardia was similar between groups: Group Mg, 11.1%, and Group C, 0% ($p=0.05$).

Postoperative VAS scores were lower in Group Mg at rest and on movement than in Group C at 6 hours ($p=0.02$ and

Table 3 Average VAS pain scores and tramadol consumption 24 h after surgery.

	Group Mg (n = 45)	Group C (n = 41)	p-value
VAS at rest 6h after surgery	2 (0–3.6)	3 (2–5)	0.02
VAS on movement 6h after surgery	4 (2–5)	5 (5–7)	0.03
VAS at rest 24h after surgery	1.2 (0–3)	2 (0–4.5)	0.12
VAS on movement 24h after surgery	4 (2–6)	4.8 (3–6)	0.29
Tramadol consumption (mg)	15.5 ± 36.6	29.2 ± 67.8	0.53

Data are expressed mean and standard deviation and median (percentile 25–75).
VAS, Visual Analogic Scale. Mann-Whitney test.

$p=0.03$, respectively). However, VAS scores were similar at 24 hours at rest ($p=0.12$) and on movement ($p=0.29$). There was no significant difference between Group Mg and Group C concerning the tramadol consumption (15.5 ± 36.6 mg and 29.2 ± 67.8 mg respectively, $p=0.53$) (Table 3).

The incidence of NVPO was similar between the two groups: Group Mg, 8.9%, and Group C, 17.1%, ($p=0.33$). The incidence of pruritus (moderate and severe) was similar between the two groups: Group Mg, 6.7%, and Group C, 0% ($p=0.24$).

Discussion

This study showed that $MgSO_4$ infusion during abdominal hysterectomy under spinal anesthesia with $100 \mu\text{g}$ ITM reduced postoperative pain scores at 6 hours but did not reduce at 24 hours. We also observed that $MgSO_4$ had no impact on tramadol consumption, and we did not find any notable adverse events.

Regional anesthesia can be preferred to general anesthesia during the perioperative period.^{6,8,14} In our service, abdominal hysterectomy is performed under spinal anesthesia with 17.5 mg hyperbaric bupivacaine and $100 \mu\text{g}$ of ITM, unless contraindicated. Although this scheme is adequate, some patients report pain of moderate to severe intensity. Pain after abdominal hysterectomy can be multifactorial: from a surgical incision, visceral pain, and particularly dynamic pain, such as during coughing and mobilization. Accordingly, several strategies for pain management have been introduced during the intraoperative and postoperative period. The administration of adjuvants to optimize postoperative analgesia and reduce painful stimuli to prevent central sensitization and amplification of postoperative pain has been used. Intravenous magnesium has been used in obstetrics for a long time to safely treat pregnant women with eclampsia and preeclampsia. It has recently been used as an adjuvant due to its analgesic properties. Although the exact mechanism is not fully understood, the analgesic properties of magnesium are based on acting as a non-competitive antagonist of NMDA receptors in the central nervous system and in the peripheral tissues.¹⁵ It also acts by regulating the influx of calcium into the cell.¹¹ Moreover, it was suggested that NMDA receptor antagonists might enhance the analgesic effect of opioids by delaying or reducing the development of acute tolerance.^{11,16}

The normal range of magnesium in plasma is $1.5\text{--}2.5 \text{ mEq.L}^{-1}$. Hypermagnesemia (serum concentrations more than 4 mEq.L^{-1}) rarely occurs in clinical medicine

unless the renal function of the patient is compromised. Further increasing magnesium serum concentrations may result in hypotension, loss of deep tendon reflex, and dizziness. Respiratory arrest and cardiac arrest occur at blood concentrations greater than 12 mEq.L^{-1} .¹¹ In this study, with $MgSO_4$ in the loading dose (50 mg kg^{-1} in for minutes) and maintenance ($15 \text{ mg kg}^{-1} \cdot \text{h}^{-1}$), six patients with the serum concentration exceeded 4 mEq.L^{-1} ($4.03\text{--}4.89$), and none of them presented any complications.

In this study, the MAP and HR were uniform over time between the two groups, without significant hemodynamic changes. These results are similar to studies of Hwang et al.¹⁷ and Agrawal et al.¹⁸ According to these authors, the pre-hydration with 500 mL of Ringer's lactate and the slow infusion of the medication could explain this hemodynamic stability. In contrast, Ryu et al.¹⁹ and Seyhan et al.²⁰ reported lower MAP and HR values in patients who received $MgSO_4$. Five cases of bradycardia (with immediate recovery after administration of atropine) were recorded in Group Mg and no case in Group C ($p=0.05$). However, bradycardia was never observed in concomitance to hypotension. According to Albrecht et al.,²¹ the incidence of bradycardia was higher in the magnesium group (RR = 1.76; 95% CI 1.01–3.07; $p=0.04$), but without an increased incidence of hypotension (RR = 1.49; 95% CI 0.88–2.52; $p=0.14$), and they reported that although bradycardia was more common after magnesium administration, there were no reports of persistent hemodynamic instability or bradycardia that did not respond to first-line pharmacologic therapy.

A systematic review carried out in 2013 by Albrecht et al.,²¹ that included two studies in which patients received spinal anesthesia and 23 in which they received general anesthesia, concluded that perioperative IV magnesium reduces opioid consumption and, to a lesser extent, pain scores in the first 24 postoperative hours. Recently, several studies have reported the benefits of IV magnesium infusion in the postoperative pain scores and opioid consumption of patients who undergone surgery under general anesthesia.^{22–27} However, the effects of magnesium on pain scores and the consumption of opioids in patients undergoing spinal anesthesia is still debated. In some studies, the patients received only bupivacaine,^{28–30} and in other studies, the patients received only bupivacaine or bupivacaine + $10\text{--}20 \mu\text{g}$ fentanyl^{18,31} and showed a consistent decrease in opioid consumption, but with a decrease in pain scores up to 4,^{28,29} 10,³⁰ and 48 hours³¹ postoperatively. In our study, there was a decrease in pain scores only in the first 6 hours postoperatively, which may reflect a more limited effect

of magnesium sulfate infusion in our patients. It is noteworthy that in the study conducted by Agrawal et al.,¹⁸ in patients undergoing lower limb orthopedic surgeries, the consumption of tramadol in the group that received magnesium compared to the group that received saline was (190 ± 30 mg vs. 265 ± 48 mg; $p=0.000$). This result differs significantly from the result of our study (15.5 ± 36.6 mg vs. 29.2 ± 67.8 mg versus, $p=0.53$). We can suppose that the inflammatory response in these orthopedic surgeries is very different from hysterectomies.

To the best of our knowledge, we found only one prospective study in which patients received magnesium infusion that underwent spinal anesthesia with hyperbaric bupivacaine plus ITM, but none of them did hysterectomies. In a randomized, double-blind study, Frassanito et al.³² evaluated 40 patients undergoing total knee arthroplasty under spinal anesthesia with hyperbaric bupivacaine mixed with $100 \mu\text{g}$ ITM – 20 received magnesium infusion and 20 received saline. Ketorolac and paracetamol were routinely prescribed and received analgesic rescue with received patient-controlled analgesia with morphine in the postoperative period. These authors found neither decreased pain scores nor a decrease in morphine consumption and concluded that a multimodal analgesic approach could partially hide the effect of MgSO_4 . We conjecture that, in our study, multimodal analgesic approach to pain, which included the administration of dexamethasone 10 mg in a single dose, in addition to the administration of ketoprofen 100 mg and dipyrone 2 g at regular intervals within 24 hours of the operation may have mitigated the effects of infusion of MgSO_4 .

Our study showed an incidence of PONV of approximately 9% in the Group Mg and 17% in the Group C ($p=0.33$). Interestingly, the systematic review carried out in 2018 by Peng et al.,³³ suggested that the administration of IV magnesium in patients undergoing orthopedic surgeries could decrease nausea (Relative Risk – RR=0.32, Confidence Interval – 95% CI 0.12–0.82) and vomiting (RR=0.38, 95% CI 0.15–0.92).

The present study has some limitations. First, it was decided not to exclude women with previous cesarean delivery, but this decision may hinder the external validation of our results. Second, it was not evaluated the effect of magnesium on inflammatory activity. Third, it was not investigated the potential action of magnesium ion on prolonging the duration of sensory block of spinal anesthesia with bupivacaine. Finally, it was analyzed the data at a single medical center; therefore, the generalizability of this study may be limited.

Conclusion

In conclusion, we found that intraoperative administration of MgSO_4 (50 mg kg^{-1} boluses followed by $15 \text{ mg kg}^{-1} \text{ h}^{-1}$ continuous infusions) during AH under spinal anesthesia with $100 \mu\text{g}$ ITM reduced postoperative pain scores at 6 hours (at rest and on movement) but did not reduce at 24 hours. We also found that magnesium sulfate had no impact on tramadol consumption, with any notable adverse events. More studies should be performed to evaluate the potential antinociceptive effect of MgSO_4 , in scenarios where a multimodal analgesia approach was employed.

Conflicts of interest

The authors declare no conflicts of interest.

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