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CLINICAL RESEARCH

Analgesic effect of magnesium sulfate during total intravenous anesthesia: randomized clinical study

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Abstract
Introduction and objective: : Opioids have usually been used as intraoperative analgesic components, regardless of the many adverse effects they are associated with, such as nausea, vomiting, respiratory depression, and hyperalgesia. Several approaches have been investigated to reduce doses used, and magnesium sulfate has been shown to be a valuable analgesic adjunct. The main objective of the present trial was to evaluate the effectiveness of magnesium sulfate as the chief intraoperative analgesic, and the secondary objectives were to assess propofol consumption, postoperative analgesia, and intraoperative hemodynamic stability.
Methods: In this prospective, double-blind trial, 50 patients scheduled to undergo post-bariatric abdominoplasty under general intravenous anesthesia were divided into two groups, to receive remifentanil or magnesium sulfate as intraoperative analgesic. Fentanyl 1 $\mu g\ kg^{-1}$ was the rescue analgesic.
Results: Among the patients in the group receiving Magnesium Sulfate (MSG), 64% did not need supplemental analgesia and none of the patients in the Remifentanil Group (RG) required fentanyl. MSG patients showed propofol consumption 36.6% higher (guided by the Bispectral Index – BIS). MSG patients consumed significantly less ephedrine (mean $\pm$ SD) than RG patients, respectively 1.52 $\pm$ 4.38 mg and 10 $\pm$ 10.39 mg, $p < 0.001$. Mean values of blood concentrations of magnesium were comparable to values previously described in the literature.
Conclusion: Magnesium sulfate is a safe and effective option for intraoperative analgesia, when avoiding or decreasing opioid use is required.

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Introduction

Opioids have been used as analgesic components of anesthesia,[1] especially after the development of fentanyl in 1959.[2] Subsequently, other synthetic opioids, such as alfentanil, sufentanil and remifentanil, were launched with the expansion of the group.[3] Over time, several side effects related to opioids have been added, such as hyperalgesia[4–10] and delayed return of bowel motility,[1–13] in addition to suspicion of facilitating growth and spread of tumor cells.[14–16] These drawbacks stimulated the investigation of new options for perioperative analgesics.[17–19]

Magnesium sulfate has been reported as a valuable adjunct agent in anesthesia, improving the intraoperative analgesic profile, reducing postoperative hyperalgesia, nausea, vomiting, and the consumption of perioperative analgesics.[20–25]

The present trial aimed to evaluate the effectiveness of magnesium sulfate as an alternative for intraoperative analgesia, compared to the use of remifentanil. The hypothesis was that magnesium sulfate could provide satisfactory intraoperative analgesia. Fentanyl (1 $\mu g\ kg^{-1}$) was used as an intraoperative rescue analgesic. The outcomes used to compare the differences between the group receiving Magnesium Sulfate (MSG) and the group receiving Remifentanil (RG) were intraoperative consumption of rescue fentanyl, alongside systolic blood pressure changes observed after tracheal intubation and surgical incision. As secondary outcomes, we compared the groups regarding postoperative analgesia and intraoperative consumption of propofol and ephedrine. Plasmatic levels of magnesium (Mg) were also measured before, during, and after surgery.

Methods

This prospective, controlled, double-blind trial with a sample randomly allocated into two groups evaluated the efficacy of magnesium sulfate as an analgesic component in total intravenous anesthesia. Recruitment was initiated after approval by the Research Ethics Committee of the Universidade de Taubaté (Certificate of Submission to Ethical Appreciation – CAAE: 52621616.6.0000.5501, approved according to opinion nº 1.464.016), São Paulo, Brazil, and the Ethics Committee of the Santos Dumont Hospital, in São José dos Campos, São Paulo. The study sample was recruited from the population of patients scheduled for post-bariatric abdominoplasty surgery, of both genders, ASA physical status I or II, with Body Mass Index (BMI) < 35 kg m^{-2}, capable of answering questions related to the quality of analgesia or adverse effects, and that voluntarily accepted to participate in the study and signe the Informed Consent Form (ICF). We excluded from the study patients with allergies to any medications included in the study protocol, patients presenting moderate to severe heart rhythm disorders, patients expected to have difficult airway management, patients with neuromuscular diseases, and patients with renal failure.

Anesthetic technique

All study participants were monitored with continuous electrocardiography, non-invasive arterial Blood Pressure (BP), pulse oximetry, capnography (GE anesthesia machine, model Aysis, series ANAM 01294, Datex Ohmeda Inc, Madison WI 53707-7550, USA), neuromuscular paralysis with train of four stimuli applied to the ulnar nerve/adductor pollicis muscle (TOF-NMT Mechano Sensor Ref. 888414, GE, Datex Ohmeda Inc, Madison WI 53707-7550, USA), and depth of hypnosis using the Bispectral Index (BIS – Aspect Medical A 2000 BIS XP, Aspect Medical Systems Inc. Newton, MA 02464, USA). Blood samples were collected from all participants to measure magnesium plasma levels at the following times: before induction of anesthesia (during venipuncture), immediately before skin incision, before tracheal extubation and after awakening from anesthesia.

After recording baseline monitoring data, peripheral venous access was performed with a 20G or 18G intravenous catheter and the blood sample for Mg measurement was collected. Then a 15-minute intravenous (IV) infusion of a concealed 250 mL Saline Solution (SS) was initiated, containing plain SS for patients of the Remifentanil Group (RG) or magnesium sulfate added for patients of the Magnesium Sulfate Group (MSG). Concomitantly, dipyrone 2 g, clonidine 2 $\mu g\ kg^{-1}$, dexamethasone 4 mg, ranitidine 50 mg, cefazolin 2 g, ondansetron 4 mg, and ketoprofen 100 mg were administered. After the end of the SS infusion, a syringe pump was started with an infusion rate set at 0.2 mL $kg^{-1}\ h^{-1}$ of previous prepared concealed solution syringes. According to the solution preparation, the infusion rate corresponded to an infusion of magnesium sulfate of 10 mg $kg^{-1}\ h^{-1}$ for MSG patients, or remifentanil 0.2 $\mu g\ kg^{-1}\ min^{-1}$ for RG patients. Monitoring data were recorded, 1.5 mg kg^{-1} of lidocaine was administered and the propofol target controlled infusion was initiated with the target concentration set at 4 $\mu g\ mL^{-1}$ (Marsh effect model). When the BIS reached values between 40 and 60, the infused propofol dose and the time between propofol infusion initiation and BIS $\leq$ 60 was recorded. Then, after neuromuscular function monitor calibration, a 0.15 mg kg^{-1} cisatracurium dose was administered. Orotracheal Intubation (IOT) was performed with TOF 4 or less, if the laryngoscopy was satisfactory, and the time to reach T0 was recorded. After IOT, the propofol infusion was set to keep BIS between 40 and 60 and the infusion of concealed solution was controlled for BP and heart rate (HR) values not higher or lower than 20% of baseline values. BP elevations with BIS between 40 and 60 were treated with an increase in the infusion speed of the concealed solution. If the infusion rate reached 0.4 mL $kg^{-1}\ h^{-1}$ (twice the initial rate) and BP remained more than 20% above baseline for more than 2 minutes, boluses of 1 $\mu g\ kg^{-1}$ of fentanyl were administered, until BP control. Conversely, when BP decreased to values lower than 20% of baseline and did not respond to a reduction in the rate of infusion of the covered solution, 5 mg IV ephedrine was administered. Atropine (0.5 mg IV) was given if HR was below 30% of baseline values associated with arterial hypotension, or when HR was below 45. Complementary doses of cisatracurium (0.03 mg kg^{-1}) were administered if TOF $\geq$ 1, if muscle relaxation was requested by the surgeon, or in case of patient respira-

tory effort. The requirement of full muscle paralysis and immobilization to protect rectus abdominis plication precluded a perfect assessment of cisatracurium consumption, guided exclusively by TOF. Both propofol and concealed solution infusions were discontinued at completion of surgery. When monitoring TOF $\geq$ 2, participants received neostigmine 0.03 mg kg^{-1}, associated with atropine 0.013 mg kg^{-1}. The following data were recorded: first supplementary dose of cisatracurium, last dose of cisatracurium, time between the last dose and tracheal extubation, time between the last dose and TOF $\geq$ 90%, time between propofol infusion initiation and BIS $\leq$ 60, and time between propofol discontinuation and BIS $\geq$ 60. We recorded total consumption of propofol, total consumption of concealed solution, total consumption of fentanyl, total consumption of ephedrine, and pain upon awakening. The presence of pain upon awakening $\geq$ 4 (Verbal Numeric Scale – VNS, from 0 to 10) was treated with dipyrone 2 g and, if the pain persisted, morphine 2 mg every 20 minutes was given until pain relief or up to the third morphine dose. Afterwards, a patient-controlled analgesia pump (PCA – Hospira GemStar® Hospira Inc pump; Lake Forest, Illinois, USA) using morphine was initiated.

To minimize bleeding and promote postoperative analgesia before skin incision the surgeon infiltrated the subcutaneous abdominal region of each patient with saline solution containing lidocaine (0.4 mg mL^{-1}) and adrenaline (1:500,000).

The primary outcome was change observed in Systolic Blood Pressure (SBP) pre- and post-tracheal intubation, and pre- and post-skin incision. Secondary outcomes analyzed were fentanyl consumption as a rescue analgesic in patients showing increase in blood pressure that did not respond to increased infusion of the concealed analgesic, intraoperative consumption of propofol, cisatracurium and ephedrine, and postoperative consumption of dipyrone, morphine, and ondansetron. Pre, intra, and postoperative plasma levels of magnesium were also measured.

Sample calculation

Olgun et al. evaluated the use of magnesium sulfate in balanced anesthesia for laparoscopic cholecystectomy and found a significant reduction in the consumption of desflurane (46.7 $\pm$ 13.5 mL vs. 59.9 $\pm$ 21 mL in the control group; $p < 0.05$).[26] As we found no study using magnesium sulfate as the only intraoperative analgesic, we based ourselves on those numbers, and we estimated that, for our trial, for a 95% confidence level and 80% power, a sample of 19 patients would be sufficient (calculation of quantitative variables – Pocock SJ)[27] in each group. We included 25 patients to compensate for losses.

The consumption of propofol (dose of induction and maintenance), cisatracurium, fentanyl, and ephedrine were recorded intraoperatively, and the duration of anesthesia and consumption of dipyrone, morphine, and ondansetron in the postoperative period, during hospitalization.

Data were organized on a spreadsheet (MS-Excel, version MS-Office 2013), and results were analyzed using statistical packages IBM-SPSS (Statistical Package for Social Sciences, version 26) and R 3.6.0.

The 50 participants were allocated into two groups (RG and MSG) through an electronic draw (www.random.org). Blinding of participants and team was performed using 50 opaque envelopes numbered from 1 to 50, with the name of the group and the corresponding formula inside, according to the result of the draw. Only one team member had access to the draw and the internal identification of each envelope. This member kept the draw secret for any necessary checking and did not participate in the remaining part of the study. In the operating room, a previously trained nurse was responsible for the opaque envelope corresponding to the patient and prepared the study solution, which was kept concealed to the patient and other professionals. For the MSG, 250 mL of Saline Solution (SS) were prepared with 10% magnesium sulfate 40 mg kg^{-1} (0.4 mL kg^{-1}) and two syringes, each with 33 mL of magnesium sulfate diluted to 5% in SS (50 mg mL^{-1}). For the RG, 250 mL of plain SS and two syringes were prepared, each with 33 mL of SS with 2 mg of remifentanil (60 μg mL^{-1}).

Results

The flow of participants in the study is shown on the CONSORT flowchart (Figure 1). Of the 50 participants, 5 were excluded from the RG, and 2 from the MSG. The RG had 95% women (19, out of 20 participants) versus 91.3% in the MSG (21, out of 23 participants). In the RG, 18 patients (90%) were ASA I classification, versus 16 patients (69.57%) in the MSG. Table 1 shows the similarity between the groups regarding anthropometric characteristics and duration of anesthesia.

Primary outcomes

The association between the variable systolic pressure and treatment upon tracheal intubation and skin incision times was assessed using a two-way ANOVA with repeated measures, since the data held the necessary assumptions for the application of this parametric technique.

The initial assessment of the effect of tracheal intubation on blood pressure indicated an interaction between treatment and time. While participants in the RG presented a reduction in systolic blood pressure after orotracheal intubation, participants in the MSG showed an increase in systolic pressure. The two-way ANOVA repeated measures confirmed the Treatment*Time interaction effect (p = 0.028), with an effect size of 0.230. That is, the mean systolic pressure varied differently over time, depending on the type of treatment (RG or MSG). In the post hoc assessment, shown in Table 2, it is evident that there is no significant difference in the variation in systolic blood pressure between the pre- and post-tracheal intubation times between the groups.

In assessing the effect of skin incision on systolic blood pressure, the behavior was similar to that observed with tracheal intubation. There was a minor decrease in pressure in RG patients, while MSG patients showed an increase in systolic pressure after skin incision. After applying the two-way ANOVA, we found this effect with statistical significance (p = 0.001) and effect size = 0.460. Despite the statistical difference in blood pressure behavior in the two groups ($p < 0.05$), there was only a significant difference in the MSG between the timepoints studied (p = 0.002). Table 2

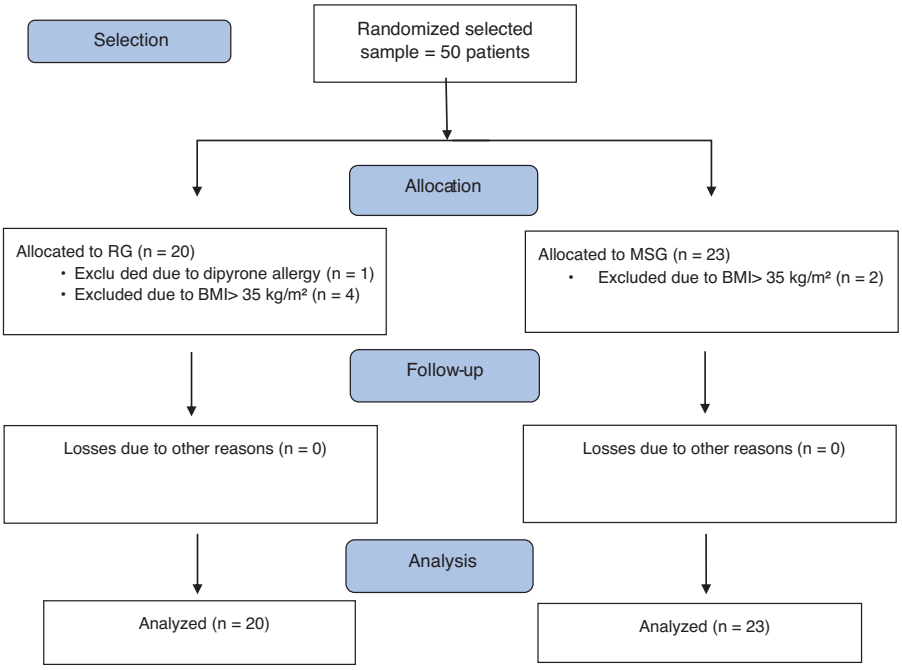

Figure 1 CONSORT flowchart of study participants.

Table 1 Anthropometric data and duration of anesthesia.

Variable/Group		Mean	SD
Age (years)	RG	37.15	10.33
	MSG	39.87	6.57
BMI (m kg^{-2})	RG	25.74	2.90
	MSG	26.03	2.41
Weight (kg)	RG	70.84	10.34
	MSG	71.94	11.36
Height (m)	RG	1.66	0.07
	MSG	1.66	0.09
Duration of anesthesia (min)	RG	150.30	18.91
	MSG	159.39	22.03

BMI, Body Mass Index; SD, Standard Deviation; RG, Remifentanil Group; MSG, Magnesium Sulfate Group.

Table 2 Descriptive statistics and confidence interval for systolic blood pressure pre- and post-tracheal intubation, and before and after skin incision (treatment vs. time).

	Time	Mean	Standard error	95% Confidence Interval	
				Upper limit	Lower limit
RG	Pre-intubation	10.4.55	2.815	98.658	110.442
	Post-intubation	96.35	3.785	88.427	104.273
MSG	Pre-intubation	102.55	2.910	96.460	108.640
	Post-intubation	112.75	5.706	100.807	124.693
RG	Before incision	93.50	2.684	87.883	99.117
	After incision	90.65	2.494	85.429	95.871
MSG	Before incision	101.35	2.844	95.396	107.304
	After incision	115.60	7.723	103.622	127.578

RG, Remifentanil Group; MSG, Magnesium Sulfate Group. Two-way ANOVA.

also shows that there was no statistical difference between the groups.

As expected, RG patients did not require supplemental analgesia (with fentanyl), while 8 patients (34.7%) from MSG had to receive fentanyl at doses ranging between 1 and 3 $\mu g\ kg^{-1}$ throughout the procedure. Table 3 shows fentanyl consumption in the MSG.

Secondary outcomes

The RG showed significantly higher ephedrine consumption (Table 3). For the MSG, propofol consumption for anesthesia maintenance was significantly higher than for the RG (Table 3). There was no difference between groups regarding the dose of propofol for induction.

As expected, mean magnesium plasma concentration did not change significantly for RG patients. Table 4 shows the increase in magnesium plasma concentration in MSG patients.

Using a verbal pain scale (0, no pain to 10, worst pain imaginable) we recorded pain scores at anesthesia awakening, and 6 hours later. Then, patients were followed up for 3 days after hospital discharge by telephone interview to assess pain at rest and dynamic pain in the morning and in the afternoon, using a verbal scale from 0 to 10. Table 5 shows the results. As the variable is categorical, non-parametric analysis of distribution and median was performed, using the Mann–Whitney *U* test and the Median test. There was no statistical difference between the groups for pain at rest or dynamic pain, at any of the timepoints analyzed, except for pain at rest in the first postoperative morning, when MSG patients revealed lower pain scores ($p = 0.031$).

Discussion

The hemodynamic stability and comparable performance of patients in the groups receiving remifentanil or magnesium sulfate as intraoperative analgesic unfolds a new option for reducing the use of opioids and consequently their side effects. Systolic arterial pressure was statistically similar after orotracheal intubation and surgical incision in both groups. Magnesium sulfate showed efficacy in controlling pain and autonomic responses during surgery. The groups were statistically similar in postoperative analgesia, which was a surprise, since we expected some degree of hyperalgesia induced by remifentanil.

In patients undergoing regional anesthesia, with or without sedation, pain intensity is assessed using appropriate scales. In general anesthesia, autonomic responses are used empirically as a means of assessing the adequacy of analgesia, with signs such as sweating, high blood pressure and tachycardia. They are low-specificity predictors, easily masked by medications (beta-blockers, for example) and display interpersonal variability.

The hemodynamic stability observed in both groups may have resulted from adequate analgesia in both groups.[22,28] The low fentanyl consumption in the MSG suggests intraoperative analgesia promoted by magnesium sulfate. Of the 23 patients in the MSG, 8 (34.8%) required analgesic supplementation, but low doses of fentanyl (1 to 3 $\mu g\ kg^{-1}$) were used, and 64% of patients in the same group had adequate intraoperative analgesia with magnesium sulfate.[21] This shows the valuable contribution offered by magnesium sulfate when it is part of multimodal analgesia, which obviously has the capacity to further reduce intraoperative opioid requirements. RG patients received the routinely used mean dose of remifentanil, which provides adequate analgesia due to its proven efficacy, and avoided additional consumption of opioids (fentanyl).[7]

New algorithms have been studied in the pursuit for a more sensitive and specific assessment of intraoperative analgesia, such as monitoring the surgical plethysmography index,[29–33] which may be a valuable tool in future studies for more validated assessment of magnesium sulfate analgesia.

The more intense autonomic depression, the potentiation of the effect of hypnotics and the superior anti-nociceptive efficacy associated with remifentanil resulted in a statistically lower and higher consumption of, respectively, propofol and ephedrine in RG compared to MSG patients. For the RG, 60% of the patients required ephedrine for BP control, against 13% of the patients in the MSG, probably for the same reason described above.[23,28] Here a relevant issue is comparing the advantages and disadvantages of reducing opioid use at the expense of increased consumption of propofol.

The gradual decline in Systolic Blood Pressure (SBP) up to the first blood pressure measurement after skin incision may have occurred due to the local anesthetic solution infiltration by the surgeon associated with lack of nociceptive stimulus, as SBP measured values that soon returned to an acceptable range, and most patients did not need vasoactive medication in both groups.

The dose of magnesium sulfate used was based on studies assessing it as an adjunct analgesic,[34–38] which was not the objective in this investigation. After years of using magnesium sulfate in their practice, however, the authors realized how much they succeeded reducing opioid dose in post-bariatric abdominoplasty surgeries with a safe and controlled approach. The option to use magnesium sulfate to replace opioids attempts to determine the extent of the analgesia produced by magnesium sulfate, which is so widely recognized in other situations.

An interesting observation in this study was the recovery time from hypnosis and neuromuscular block. As the groups were blinded, it would not be possible to discontinue the infusion of the concealed solution too early, to avoid any recovery delay. Thus, the infusions of propofol and the concealed solution were interrupted at surgery completion, preventing, in the case of the RG, intraoperative analgesia from being interrupted too soon. This did not result in a significant difference in awakening or muscle function recovery when groups were compared. Although it was not the objective of the study, it would be interesting to investigate this finding.

Postoperative pain scores were surprisingly comparable, since some degree of hyperalgesia was expected in patients receiving remifentanil and greater protection against postoperative pain due to the blocking effect of NMDA receptors. A possible explanation for this similar finding may be the intra-operative lidocaine infiltration, which may be a source of further investigation in the future.

Table 3 Propofol, fentanyl and ephedrine consumption.

Variables/Group		n	Mean	SE	*p*-value
Ephedrine (mg)	RG	20	10.00	2.32	0.001[a]
	MSG	23	1.52	0.91	
Fentanyl (μg)	RG	20	0.00	0.00	0.004[a]
	MSG	23	49.78	16.76	
Propofol induction dose (mg kg^{-1})	RG	19	1.37	0.04	0.786
	MSG	21	1.34	0.06	
Total of Propofol (μg kg^{-1} min^{-1})	RG	20	90.07	4.46	0.000[a]
	MSG	23	123.34	3.27	

RG, Remifentanil Group; MSG, Magnesium Sulfate Group; SE, Standard Error.
[a] $p < 0.5$, statistical significance; Mann-Whitney test.

Table 4 Magnesium blood concentration (Mg/dL) during the study.

Variable/Group		n	Mean	SE	*p*-value
T0	RG	14	1.93	0.04	0.936
	MSG	12	1.94	0.04	
T1	RG	14	1.70	0.05	< 0.001[a]
	MSG	12	3.33	0.21	
T2	RG	14	1.66	0.05	< 0.001[a]
	MSG	12	3.27	0.14	
T3	RG	14	1.74	0.06	< 0.001[a]
	MSG	12	3.13	0.18	

RG, Remifentanil Group; MSG, Magnesium Sulfate Group; T0, Immediately before anesthesia; T1, Before skin incision; T2, Pre-tracheal extubation; T3, Immediately after awakening from anesthesia.
Due to mishandling of some samples only 14 patients from RG and 12 from MSG had blood concentration measurements at every moment of the study.
[a] $p < 0.05$; statistical significance.

Table 5 Pain scores at timepoints analyzed.

	Awakening	6 hours	AM 1	PM 1	AM 2	PM 2	AM 3	PM 3
At rest RG	3.7	0.79	1.4	1	0.65	0.05	0.35	0.4
At rest MSG	3.22	0.86	0.35	0.74	0.54	0.3	0.26	0.22
Dynamic RG			3.05	3.8	2.85	2	1.95	1.6
Dynamic MSG			2.54	2.96	2.37	1.74	1.52	1.13

RG, Remifentanil Group; MSG, Magnesium Sulfate Group.
Mann-Whitney U test.

The Mg plasma concentration remained stable during the study, with statistically not significant reduction after anesthetic induction in the RG group. For MSG patients, the Mg plasma concentration rose above the maximum limits of normality, without reaching toxic levels, as previously reported.[39] Limiting the magnesium sulfate infusion duration could be an alternative to prevent excessively high Mg plasma concentrations.

One limitation of this trial is that the results are limited to post-bariatric abdominoplasty (extra-peritoneal procedure). The significantly higher consumption of propofol in MSG patients may have compromised the blinding of the study for the provider of anesthesia and for the researcher who analyzed the data of the groups. One shortcoming is that the sample size was small to analyze the secondary outcomes.

In the present study that assessed patients submitted to post-bariatric abdominoplasty under target-controlled intravenous general anesthesia, magnesium sulfate proved to be a safe and valuable analgesic agent that matched procedure requirements. Nevertheless, we need investigations evaluating larger samples to validate the findings of this study.

Conclusion

We conclude that magnesium sulfate is a safe and effective option for intraoperative analgesia for patients submitted to

post-bariatric abdominoplasty. Its use has shown efficiency in reducing opioid consumption.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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