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 μg 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 ± SD) than RG patients, respectively 1.52 ± 4.38 mg and 10 ± 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, especially after the development of fentanyl in 1959. Subsequently, other synthetic opioids, such as alfentanil, sufentanil and remifentanil, were launched with the expansion of the group. Over time, several side effects related to opioids have been added, such as hyperalgesia and delayed return of bowel motility, in suspicion to facilitating growth and spread of tumor cells. These drawbacks stimulated the investigation of new options for perioperative analgesics.

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. 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 μg 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 n\(^{2}\) 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 sign 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 Mechoan 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, dipyrrone 2 g, clonidine 2 μg 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 μg 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 μg 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 ≤ 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 μg 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 ≥ 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 ≥ 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 ≥ 90%, time between propofol infusion initiation and BIS ≤ 60, and time between propofol discontinuation and BIS ≥ 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 ≥ 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 ± 13.5 mL vs. 59.9 ± 21 mL in the control group; p < 0.05).⁶ 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).⁷ 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
Ran domized selected sample = 50 patients

Allocated to RG (n = 20)
• Excluded due to dipyridamole allergy (n = 1)
• Excluded due to BMI >35 kg/m² (n = 4)

Allocated to MSG (n = 23)
• Excluded due to BMI >35 kg/m² (n = 2)

Follow-up
Losses due to other reasons (n = 0)

Analysis
Analysed (n = 20)

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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     | 10.455 | 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. 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. 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).

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, 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. 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, 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<sup>a</sup> |
| MSG                   | 23 | 1.52 | 0.91|         |
| Fentanyl (μg)         |    |      |     |         |
| RG                    | 20 | 0.00 | 0.00| 0.004<sup>a</sup> |
| MSG                   | 23 | 49.78| 16.76|         |
| Propofol induction    |    |      |     |         |
| RG                    | 19 | 1.37 | 0.04| 0.786   |
| MSG                   | 21 | 1.34 | 0.06|         |
| Total of Propofol     |    |      |     |         |
| (μg kg<sup>-1</sup> min<sup>-1</sup>) | 20 | 90.07| 4.46| 0.000<sup>a</sup> |
|                       |    |      |     |         |

RG, Remifentanil Group; MSG, Magnesium Sulfate Group; SE, Standard Error.
<sup>a</sup> p < 0.05, 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|         |
| MSG                  | 12 | 3.33 | 0.21|         |
| T2                   |    |      |     |         |
| RG                   | 14 | 1.66 | 0.05|         |
| MSG                  | 12 | 3.27 | 0.14|         |
| T3                   |    |      |     |         |
| RG                   | 14 | 1.74 | 0.06|         |
| 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.
<sup>a</sup> 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. 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.

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References
1. Dunde JW, Moore J. Alterations in response to somatic pain associated with anaesthesia. Br J Anaesth. 1960;32:453–9.
2. Stanley TH. The fentanyl story. J Pain. 2014;15:1215–26.
3. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician. 2008;11:5133–53.
4. Lee M, Silverman S, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14:145–61.
5. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance. Anesthesiology. 2008;93:409–17.
6. Kissin I, Bright CA, Bradley EL. Acute tolerance to continuously infused alfentanil: The role of cholecystokinin and N-methyl-D-aspartate-nitric oxide systems. Anesth Analg. 2000;91:110–6.
7. Zhao M, Joo DT. Enhancement of spinal N-methyl-D-aspartate receptor function by remifentanil action at δ-opioid receptors as a mechanism for acute opioid-induced hyperalgesia or tolerance. Anesthesiology. 2008;109:308–17.
8. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. Br J Anaesth. 2014;112:991–1004.
9. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. Clin J Pain. 2008;24:479–96.
10. Hahnenkamp K, Nollet J, Van Aken HK, et al. Remifentanil directly activates human N-methyl-D-aspartate receptors expressed in Xenopus laevis oocytes. Anesthesiology. 2004;100:1531–7.
11. Chen W, Chung HH, Cheng JT. Opiate-induced constipation related to activation of small intestine opioid μ2-receptors. World J Gastroenterol. 2012;18:1391–6.
12. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs. 2003;63:649–71.
13. Scott MJ, Baldini G, Fearon KCH, et al. Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery, part 1: Pathophysiological considerations. Acta Anaesthesiol Scand. 2015;59:1212–31.
14. Bimonte S, Barbieri A, Rea D, et al. Morphine promotes tumor angiogenesis and increases breast cancer progression. Biomed Res Int. 2014;2014:1–8.
15. Wang K, Qi X, Wang Y, et al. Effect of mu agonists on long-term survival and recurrence in nonsmall cell lung cancer patients. Medicine (Baltimore). 2015;94:1–9.
16. Heaney A, Buggy DJ. Can analgesic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth. 2012;109:17–28.
17. Bakam M, Umutoğlu T, Topuz U, et al. Anesthesia venosa total livre de opioides, com infusões de propofol, dexmedetomidina e lidocaína para colecistectomia laparoscópica: Estudo prospectivo, randomizado e duplo-cego. Braz J Anesthesiol. 2015;65:191–9.
18. Kim DJ, Bengali R, Anderson A. Opioid-free anesthesia using continuous dexmedetomidine and lidocaine infusions in spine surgery. Korean J Anesthesiol. 2017;70:652–3.
19. Bashá I. A systematic analysis on opioid-free general anesthesia versus opioid-based general anesthesia for bariatric surgery. Nurse Anesthesia Capstones. 2017;9:1–21.
20. Telci L, Esen F, Akcora D, et al. Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements. Br J Anaesth. 2002;89:594–8.
21. Altan A, Turgut N, Yildiz F, et al. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery. Br J Anaesth. 2005;94:438–41.
22. Seyhan TO, Tugrul M, Sungur MO, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. Br J Anaesth. 2006;96:247–52.
23. Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia. 2006;61:1058–63.
24. Albrecht E, Kirkham KR, Liu SS, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: A meta-analysis. Anaesthesia. 2013;68:79–90.
25. Arumugam S, Lau CSM, Chamberlain RS. Perioperative adjunct magnesium decreases postoperative opioid requirements – A meta-analysis. Int J Clin Med. 2016;7:297–308.
26. Olgun B, Oguz G, Kaya M, et al. The effects of magnesium sulphate on desflurane requirement, early recovery and postoperative analgesia in laparoscopic cholecystectomy. Magnesium Res. 2012;25:72–8.
27. Pocock SJ. The size of a clinical trial. In: Pocock SJ, editor. Clinical trials: a practical approach. Chinchester: John Wiley & Sons; 1983. p. 123–41.
28. Mendonça FT, De Queiroz LM da GM, Guimarães CCR, et al. Effects of lidocaine and magnesium sulfate in attenuating hemodynamic response to tracheal intubation: single-center, prospective, double-blind, randomized study. Braz J Anesthesiol. 2017;67:50–6.
29. Wennervirta J, Hynynen M, Koivusalo AM, et al. Surgical stress index as a measure of nociception/antinociception balance during general anaesthesia. Acta Anaesthesiol Scand. 2008;52:1038–45.
30. Gruenewald M, Meybohm P, Illies C, et al. Influence of different remifentanil concentration on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. Br J Anaesth. 2009;103:586–93.
31. Illies G, Gruenewald M, Ludwigs J, et al. Evaluation of the surgical stress index during spinal and general anaesthesia. Br J Anaesth. 2010;105:533–7.
32. Chen X, Thee C, Gruenewald M, et al. Comparison of Surgical Stress Index-guided Analgesia with Standard Clinical Practice during Routine General Anaesthesia. Anesthesiology. 2010;112:1175–83.
33. Mustola S, Toivonen J. Effect-sıte concentration of remifentanil attenuating surgical stress index responses to intubation of the trachea. Anaesthesia. 2010;65:581–5.
34. Koinig H, Wallner T, Marhofer P, et al. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg. 1998;87:206–10.
35. Kara H, Sahin N, Ulusan V, et al. Magnesium infusion reduces perioperative pain. Eur J Anaesthesiol. 2002;19:52–6.
36. Hoi JC, Yoon KB, Um DJ, et al. Intravenous magnesium sulfate administration reduces Propofol infusion requirements during maintenance of Propofol-N2O anaesthesia. Anesthesiology. 2002;97:1137–41.
37. Cizmeci P, Ozkose Z. Magnesium sulphate as an adjuvante to total intravenous anesthesia in septorhinoplasty: a randomized controlled study. Aesth Plast Surg. 2007;31:167–73.
38. Ryu JH, Sohn LS, Do SH. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. Br J Anaesth. 2009;103:490–5.
39. Germano Filho PA, Cavalcanti IL, Barrucand L, et al. Effect of magnesium sulphate on sugammadex reversal time for neuromuscular blockade: A randomised controlled study. Anaesthesia. 2015;70:956–61.