Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery

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Background. In this double-blind, randomized, placebo-controlled study we compared the effects of three different dose regimens of magnesium on intraoperative propofol and atracurium requirements, and postoperative morphine consumption in patients undergoing gynaecological surgery.

Methods. Eighty women were allocated to four equal groups. The control group received normal saline; magnesium groups received 40 mg kg\(^{-1}\) of magnesium before induction of anaesthesia, followed by i.v. infusion of normal saline, magnesium 10 mg kg\(^{-1}\) h\(^{-1}\) or magnesium 20 mg kg\(^{-1}\) h\(^{-1}\) for the next 4 h. Propofol infusion was targeted to keep bispectral index values between 45 and 55. Postoperative analgesia was achieved using PCA with morphine.

Results. Magnesium groups required significantly less propofol [mean (SD) 121.5 (13.3), 102.2 (8.0) and 101.3 (9.7) mg kg\(^{-1}\) min\(^{-1}\) respectively] than the control group (140.7 (16.5) mg kg\(^{-1}\) min\(^{-1}\)). Atracurium use was significantly higher in the control group than magnesium groups [0.4 (0.06) vs 0.34 (0.06), 0.35 (0.04), 0.34 (0.06) mg kg\(^{-1}\) h\(^{-1}\) respectively]. Morphine consumption was significantly higher in control group than magnesium groups on the first postoperative day [0.88 (0.14) vs 0.73 (0.17), 0.59 (0.23), 0.53 (0.21) mg kg\(^{-1}\) respectively]. The heart rate was lower in magnesium groups and 20 mg kg\(^{-1}\) h\(^{-1}\) infusion group demonstrated the lowest values.

Conclusion. Magnesium 40 mg kg\(^{-1}\) bolus followed by 10 mg kg\(^{-1}\) h\(^{-1}\) infusion leads to significant reductions in intraoperative propofol, atracurium and postoperative morphine consumption. Increasing magnesium dosage did not offer any advantages, but induced haemodynamic consequences.

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Complementary goals of this investigation were to evaluate whether increasing the infusion rate of magnesium would affect use of atracurium, haemodynamic variables, early recovery profile, postoperative pain and morphine consumption.

Methods
The Institutional Ethics Committee approved this study and written informed consent was obtained from each patient.

Power analysis ($\alpha=0.01$ and $\beta=0.05$) suggested that a sample size of 11 patients per group was needed to detect a 20% reduction in intraoperative propofol requirements. Eighty women, ASA I or II, aged 25–60 yr, undergoing elective hysterectomy with or without salpingo-oophorectomy through Pfannenstiel incision as the first case of the day were studied. Exclusion criteria were age >60 yr, hepatic, renal, respiratory or cardiac dysfunction, atrioventricular block, obesity (BMI $>$30), pregnancy, prior treatment with calcium channel blockers and known allergy to study drugs.

On arrival in the operating room, isotonic saline infusion was started at a rate of 8–12 ml kg$^{-1}$ h$^{-1}$ and continued throughout the operations. Routine monitoring of ECG, pulse oximetry, non-invasive blood pressure was established before induction of anaesthesia (Horizon XL, Mennen Medicals Inc., Rehovot, Israel). Electrodes were applied to the patient’s forehead for monitoring the bispectral index (BIS) of the electroencephalogram (A-2000 BISTM, Aspect Medical Systems Inc., Natick, MA, USA). Neuromuscular transmission was monitored using train-of-four (TOF) supramaximal stimulations (2 Hz, 50 mA; TOF Watch SX®, Organon Ltd, Dublin, Ireland). Oesophageal temperature was recorded throughout the study and normothermia was maintained with a forced warm air device (Warm Touch® Patient Warming System, Tyco Healthcare UK Ltd, Gosport, UK).

After monitoring, patients were randomly allocated to four study groups according to the numerical order of a computer generated randomization list:

In the control group (control; $n=20$) 15 min infusion of 100 ml normal saline was given before induction of anaesthesia, followed by 4 h infusion of normal saline after tracheal intubation. The magnesium bolus group (Mg; $n=20$) 15 min infusion of 40 mg kg$^{-1}$ of magnesium sulphate in a total of 100 ml normal saline was given before induction of anaesthesia, followed by 4 h infusion of normal saline after tracheal intubation. In the other two magnesium groups (Mg+10 and Mg+20; $n=20$ each) 15 min infusion of 40 mg kg$^{-1}$ magnesium sulphate in a total of 100 ml normal saline was given before induction of anaesthesia, followed by 4 h infusion of either 10 or 20 mg kg$^{-1}$ h$^{-1}$ magnesium sulphate after tracheal intubation. The i.v. infusions were administered using injector pumps with unidentified reservoirs to assure that the observer remains blinded. Pumps were programmed to inject 0.133 ml kg$^{-1}$ h$^{-1}$ for applying standard infusion rates in all groups. In order to achieve targeted amounts of magnesium, pure magnesium solution was used in the 20 mg kg$^{-1}$ h$^{-1}$ group, whereas it was diluted in 1:1 ratio with saline in the 10 mg kg$^{-1}$ h$^{-1}$ group.

After preoxygenation for at least 2 min, anaesthesia was induced with propofol 2 mg kg$^{-1}$ and fentanyl 2 $\mu$g kg$^{-1}$ i.v. by an anaesthesiologist who was blinded to the study groups. Muscle relaxation was achieved using atracurium 0.5 mg kg$^{-1}$ and the trachea was intubated when $T_1/T_0$ ratio reached 0%. The lungs were ventilated with 60% nitrous oxide in oxygen to an end-tidal concentration of carbon dioxide between 4.6 and 5.3 kPa. Anaesthesia was maintained using i.v. propofol and fentanyl. Initial propofol infusion rate was 200 $\mu$g kg$^{-1}$ min$^{-1}$ and then it was titrated to maintain the BIS value between 45 and 55. BIS was monitored continuously and propofol infusion rate was changed by 20 $\mu$g kg$^{-1}$ min$^{-1}$ if the BIS value was out of targeted range for more than 10 s. Fentanyl was infused at a fixed rate of 2 $\mu$g kg$^{-1}$ h$^{-1}$. Atracurium boluses of 0.15 mg kg$^{-1}$ were administered when more than two responses were detected in TOF-stimulation until the start of the closure of peritoneum. During skin closure, neuromuscular block was antagonized with atropine 10 $\mu$g kg$^{-1}$ and neostigmine 20 $\mu$g kg$^{-1}$ when $T_4/T_1$ ratio reached 75% or higher.

If BIS was within the targeted range and mean arterial pressure (MAP) or heart rate (HR) exceeded 20% of baseline values, fentanyl boluses of 0.5 $\mu$g kg$^{-1}$ were given. MAP 20% lower than baseline or <60 mmHg was treated with i.v. ephedrine 5 mg. Bradycardia was defined as a HR <40 bpm and treated by atropine 10 $\mu$g kg$^{-1}$.

MAP, HR and BIS were recorded before induction of anaesthesia, during induction, before tracheal intubation, just after intubation, at 5th, 15th and then at every 15 min interval throughout the procedure. Propofol and fentanyl infusions were discontinued at the end of skin closure. The time from cessation of anaesthetics to beginning of spontaneous movements, response to verbal commands and time to extubation were recorded. The time from cessation of anaesthesia to reaching a BIS value of 70 was also recorded as BIS70.

Total use of propofol, fentanyl and atracurium was recorded. The amount of propofol infused excluding the bolus dose was divided by the patient’s body weight and total propofol infusion time. In each patient, $\mu$g kg$^{-1}$ min$^{-1}$ indicates unit of mean propofol infusion rate during the entire infusion period. The total amount of atracurium was divided by the patient’s body weight and surgery time and given as mg kg$^{-1}$ h$^{-1}$.

Patients were observed for 4 h after the completion of drug infusion for possible residual drug effects in the recovery room. Patients were evaluated by the same anaesthesiologist. Postoperative pain at rest was assessed using an 11 point numeric rating scale (NRS) (0=no pain, 10=most imaginable pain). Pain relief was achieved by patient controlled analgesia device (Abbott Pain Management ProviderTM, Abbott Laboratories, North Chicago, USA) which provided...
2 mg morphine bolus with 8 min lockout interval and no background infusion. Morphine requirements were recorded at 1st, 2nd, 4th, 12th and 24th h after operation. Postoperative sedation was evaluated using Ramsay sedation scale (1=patient is anxious and agitated or restless, or both, 2=patient is cooperative, oriented and tranquil, 3=patient responds to commands only, 4=patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5=patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6=patient exhibits no response) at postoperative 15th, 30th, 45th min, and at 1st, 2nd and 4th h. Respiratory rate, SpO2, MAP, HR and side-effects, if any, were recorded at postoperative 15th, 30th, 45th min, and at 1st, 2nd, 4th, 12th and 24th h.

**Statistical analysis**

Statistical analysis was done using SPSS 10.0 software. Comparisons between groups for demographic data, total anaesthetic and analgesic drug consumption, recovery parameters, BIS values, haemodynamic variables, SpO2 and respiratory rates were performed by using one-way ANOVA. In case of statistical significance, post hoc comparisons were made by unpaired samples t-test. Ramsay sedation scores and NRS values were compared by using Kruskal–Wallis ANOVA. In order to evaluate the changes in MAP and HR during the first 90 min of the operation (the shortest operation duration), intra-group comparisons were made by using repeated measures ANOVA. Post hoc comparisons were made by using Tukey HSD and Dunnet’s t-test. χ2 and Fisher’s exact test were performed for comparison of nausea and vomiting. The results are presented as mean (SD), except Ramsay sedation scores and NRS values, that were calculated as median (interquartile range; total range). Statistical significance was assumed for P<0.05.

**Results**

The patient characteristics in different groups are summarized in Table 1. The groups did not differ with respect to age, weight or duration of operation.

BIS values did not demonstrate significant differences between four groups. Propofol, atracurium and fentanyl consumption is presented in Table 2. The highest propofol consumption was detected in the control group; Mg+10 and Mg+20 groups did not differ with respect to the amounts of propofol consumed, however both groups needed significantly lower infusion rates of propofol than the Mg bolus group. None of the patients required additional fentanyl boluses and the consumption did not differ between the groups. Atracurium consumption was also higher in the control group when compared with the study groups, but no difference was observed between Mg, Mg+10 and Mg+20 groups.

Intraoperative MAP and HR measurements are given in Tables 3 and 4. None of the patients required ephedrine boluses. Mg+20 group had significantly lower MAP values than control group in 60th and 90th min measurements (P<0.001 and P<0.05 respectively). All magnesium groups demonstrated lower HR values than control group in almost all measurements. Mg+20 group had significantly lower HR than all other groups in the 15th min. Three patients in Mg+20 group and one patient in Mg+10 group demonstrated bradycardia, which was successfully treated with atropine injection. T4/T1 ratio was >75% and reversal of neuromuscular block was completed during skin closure in all patients. Spontaneous movements were significantly delayed in Mg+20 group when compared with control and other Mg
groups. 'Response to verbal commands' and 'extubation time' was significantly longer in Mg+10 and Mg+20 groups than control group. Mg+20 group demonstrated significantly longer 'extubation time' than the Mg group (Table 5). In contrast to those parameters, BIS70 was found to be significantly shorter in Mg than control group. Mg was highest in the control group (Table 6).

Table 6 Postoperative cumulative morphine consumption. Values are mean (sd). Mg, magnesium 40 mg kg⁻¹ bolus; Mg+10, magnesium 40 mg kg⁻¹ bolus followed by infusion at 10 mg kg⁻¹ h⁻¹; Mg+20, magnesium 40 mg kg⁻¹ bolus followed by infusion at 20 mg kg⁻¹ h⁻¹. Morphine consumption is expressed as mg kg⁻¹ h⁻¹. *P<0.05, **P<0.01 and ***P<0.001 vs control group; \(^1\)P<0.05 and \(^1\)P<0.01 vs Mg group.

Values did not also demonstrate statistically significant differences between four groups.

**Discussion**

This study demonstrates that magnesium given as a single bolus or bolus plus infusion regimen reduces intraoperative propofol requirements in patients undergoing gynaecological surgery. The extra reduction in propofol consumption obtained by using 10 mg kg⁻¹ h⁻¹ maintenance infusion of magnesium could not be augmented by increasing the infusion rate to 20 mg kg⁻¹ h⁻¹.

To our knowledge, this is the first clinical trial investigating effects of different magnesium regimens. We administered a bolus dose of 40 mg kg⁻¹, because even higher doses have already been reported to be devoid of adverse effects in several studies.6–8,11,12 The maintenance regimen of 10 mg kg⁻¹ h⁻¹ approximates the infusion rate used in almost all clinical work in this area. The higher infusion rate of 20 mg kg⁻¹ h⁻¹ was within the ranges of the standard maintenance rates used in treatment of preeclampsia and eclampsia.16,17

In the present study, single bolus of 40 mg kg⁻¹ magnesium achieved a 13.5% decrease in intraoperative propofol requirements. The decline in propofol consumption was doubled when the bolus dose was combined with 10 mg kg⁻¹ h⁻¹ infusion. Doubling the infusion rate did not supply an additional reduction in propofol use. In a recent study, Sasaki and colleagues18 demonstrated that magnesium and calcium compete at the presynaptic calcium channels and this could be responsible for the modification of anaesthetic effects. This finding is supported by previous investigations, which indicated the excitatory glutamate release mediated by presynaptic calcium channels is one of the major target sites for general anesthetics.19,20

Telci and colleagues9 demonstrated significant reductions in hourly infusion rates of propofol titrated to maintain BIS between 45 and 60 by using 30 mg kg⁻¹ bolus and 10 mg kg⁻¹ h⁻¹ magnesium infusion throughout spinal operations. Although the method of this study resembles ours, propofol infusion rates were processed hourly and remifentanil was titrated to maintain haemodynamic variables. Choi and colleagues12 were able to reduce

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Table 4 HR (beat min⁻¹) at various time intervals. Values are mean (sd). Mg, magnesium 40 mg kg⁻¹ bolus; Mg+10, magnesium 40 mg kg⁻¹ bolus followed by infusion at 10 mg kg⁻¹ h⁻¹; Mg+20, magnesium 40 mg kg⁻¹ bolus followed by infusion at 20 mg kg⁻¹ h⁻¹. *P<0.05, **P<0.01 and ***P<0.001 vs control group; \(^1\)P<0.05 and \(^1\)P<0.01 vs Mg group.

Table 5 Time to spontaneous movements, response to verbal commands, extubation time and BIS70. Values are mean (sd). Time is expressed as seconds. BIS70, time from cessation of anaesthesia to reaching a BIS value of 70; Mg, magnesium 40 mg kg⁻¹ bolus; Mg+10, magnesium 40 mg kg⁻¹ bolus followed by infusion at 10 mg kg⁻¹ h⁻¹; Mg+20, magnesium 40 mg kg⁻¹ bolus followed by infusion at 20 mg kg⁻¹ h⁻¹. *P<0.05, **P<0.01 and ***P<0.001 vs control group; \(^1\)P<0.05 vs Mg group.

Table 6 Postoperative cumulative morphine consumption. Values are mean (sd). Mg, magnesium 40 mg kg⁻¹ bolus; Mg+10, magnesium 40 mg kg⁻¹ bolus followed by infusion at 10 mg kg⁻¹ h⁻¹; Mg+20, magnesium 40 mg kg⁻¹ bolus followed by infusion at 20 mg kg⁻¹ h⁻¹. Morphine consumption is expressed as mg kg⁻¹ h⁻¹. *P<0.05, **P<0.01 and ***P<0.001 vs control group; \(^1\)P<0.05 and \(^1\)P<0.01 vs Mg group.

Values did not also demonstrate statistically significant differences between four groups.
propofol infusion rate from 167 to 81 μg kg⁻¹ min⁻¹ by using 50 mg kg⁻¹ bolus and 8 mg kg⁻¹ h⁻¹ magnesium infusion throughout gynaecological surgery. Extreme differences in propofol consumption between the present data and the study by Choi and colleagues¹² are striking. Contrary to our notably high fentanyl usage, giving no opioid in any period of anaesthesia might in part account for the higher propofol infusion rates in control group of that study. Instead of using BIS, adjusting propofol infusion according to haemodynamic changes might also contribute to distinct findings. In the second part of the study, Choi and colleagues¹² re-evaluated the effects of two different propofol infusion rates obtained from the first part on BIS values. The authors find that BIS values in the control group (40.7±3.9) were significantly lower than those in the magnesium group (57.8±7.3). They stated that similar to ketamine, magnesium administration might increase the BIS as an effect of the magnesium itself or because of lower propofol requirements or no effect of magnesium on the BIS values. This assumption might explain the relatively higher propofol infusion rates in magnesium groups of the present study in which propofol was titrated to maintain BIS. In addition, unexpectedly lower values of BIS70 in magnesium groups in the present study might supply evidence about BIS and magnesium interaction. As there is no other report on testing the effect of magnesium on BIS, it is difficult to interpret these findings.

It is well known that magnesium sulphate inhibits acetylcholine release at motor nerve terminals, thus potentiating the effects of neuromuscular blocking agents. In previous studies, prior administration of magnesium sulphate prolonged clinical duration of intermediate acting non-depolarizing neuromuscular blocking agents.²¹ ²² Our results confirm clinical studies demonstrating lower neuromuscular blocker requirements with magnesium use.⁶⁻⁹ ¹⁴ In contrast to our expectations, higher magnesium regimen did not induce further reduction in atracurium dose beyond 15% obtained with 10 mg kg⁻¹ h⁻¹.

It is known that magnesium might induce hypotension directly by vasodilatation, as well as indirectly by sympathetic blockade and inhibition of catecholamine release. However, we did not observe hypotensive episodes requiring ephedrine treatment even in the higher infusion rate group. Also, contrary to other reports⁶⁻⁹ ¹¹ ¹³ ¹⁴ there was a tendency towards lower HRs even in the bolus magnesium group, which was intensified by increasing infusion rates. Because this tendency towards bradycardia occurred only in the operative period of magnesium infusion, we should reconsider possible overuse of propofol while aiming to maintain BIS within target levels as mentioned above.

We aimed to investigate the influence of higher magnesium doses on ‘extubation time’. Although being statistically significant, we consider that a maximum 200 s delay in awakening is clinically less important.

Persistence of pain in the postoperative period is explained by activation of dorsal horn NMDA receptors with excitatory transmitters, which in turn leads to calcium entry into the cell initiating a series of central sensitization. Because magnesium has been known to produce a voltage-dependent blockade of NMDA receptors, its potential analgesic effects on postoperative opioid consumption have been widely investigated in the literature.⁶⁻⁸ ¹⁰ ¹¹ ¹³⁻¹⁵ Although the exact mechanism of the interaction between the NMDA receptor complex and opioid antinociception has not been fully elucidated, it has also been suggested that NMDA receptor antagonists potentiate the analgesic effect of opioids by delaying or reducing the development of acute tolerance.³ ²³ Prevention of perioperative hypomagnesaemia⁶⁻⁷ ¹¹ ²⁴ has also been mentioned as a contributing antinociceptive mechanism, because an inverse relationship has been demonstrated between the severity of pain and serum magnesium concentration.²⁵

Although magnesium has been used successfully to potentiate opioid analgesia and in treating neuropathic pain in experimental studies,¹⁻³ clinical trials investigating the analgesic efficacy of magnesium have shown conflicting results.⁶⁻⁸ ¹⁰ ¹¹ ¹³ In their pioneering study Tramer and colleagues⁶ reported that patients undergoing lower abdominal surgery with magnesium supplementation consumed 30% less morphine in the postoperative period compared with control patients. Similar to those clinical trials, several authors demonstrated significant reduction in postoperative fentanyl, morphine and piritramide consumption after knee, uterus and lumbar operations.⁷ ⁸ ¹³ Present data support these observations by demonstrating ~40% morphine-sparing effect of magnesium compared with control. Postoperative pain scores were similar in all groups, indicating that patients titrated themselves to a subjectively comfortable level of analgesia with morphine PCA.

Despite using relatively high magnesium and fentanyl doses, early postoperative course was uneventful. Variations in haemodynamic parameters of magnesium groups disappeared after cessation of propofol and fentanyl infusions. This finding confirms magnesium-induced potentiation of effects of fentanyl and propofol on heart and vascular bed. Similar to previous reports,⁶ ¹³ postoperative sedation did not seem to be a problem even with higher infusion rates. Correspondingly respiratory status did not vary between groups. As indicated by other authors,⁶ ¹⁰ ¹⁴ magnesium use did not offer any advantages on the incidence of nausea and vomiting.

In our study there are some limitations that should be noted. We did not measure serum and cerebrospinal fluid magnesium concentrations because of two major reasons. First, it was previously reported that intra- and extracellular magnesium concentration seems to be of no clinical relevance, as they do not accurately predict magnesium levels in other body tissues.²⁶ Moreover, similar magnesium regimens in previous studies had provided almost two-fold increases in serum magnesium concentrations.⁷ ¹¹–¹⁴

As the renal excretion is dependent on the plasma magnesium concentration, it is difficult to assume that doubling
the infusion rate produces twice the plasma magnesium concentration. Had we measured plasma levels, we might have provided additional data on the magnesium concentrations of patients treated with different regimens.

Although neuromuscular block was antagonized before beginning the assessment of recovery indices in all cases, projection of ongoing effects of the reversal might result in longer recovery times. We assumed that the potential for an overlap was true for the whole population leading to proportional increases in recovery. However, it is difficult to predict whether magnesium actually intensified such a delay in reversal on accuracy of recovery assessment in two groups in which magnesium infusion was used. If we had shown full restoration of neuromuscular transmission before recovery assessment, that would have increased the reliability of the present data.

The current study design might also be questioned because of infusing magnesium for only 4 h. Although magnesium has been used for a considerably longer period of time, we think our regimen was effective enough to provide clinically significant reductions in postoperative analgesic use.

In conclusion, magnesium 40 mg kg⁻¹ bolus + 10 mg kg⁻¹ h⁻¹ infusion regimen seems to fulfill clinical expectations of reducing the requirement for propofol and atracurium intraoperatively, and morphine after operation. Increasing magnesium dosage did not offer advantages intraoperatively, but induced haemodynamic consequences.

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