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ORIGINAL ARTICLE

Evaluation of Two Different Doses of Pre-Emptive Intravenous Magnesium Sulphate as Post-Operative Adjunct Analgesia after Gynaecological Surgery

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ABSTRAK

Kajian ini dilaksanakan untuk membandingkan keberkesanan analgesia pre-emptif intravena magnesium sulfat menggunakan dos yang berbeza terhadap kesan pengawalan kesakitan berikutan pembedahan ginekologi. Seramai 56 orang pesakit dengan Indeks Jisim Badan (BMI) <35 kg/m² yang menjalani pembedahan ginekologi direkrut kepada dua kumpulan secara rawak. Kumpulan I menerima magnesium sulfat satu ampul 2.47 g dan Kumpulan II menerima magnesium sulfat 50 mg/kg (berdasarkan berat badan) sebaik sahaja sebelum pembedahan. Tahap kesakitan dan penggunaan analgesia kawalan pesakit (PCA) morfin dibandingkan pada 30 minit, 12 jam, dan 24 jam selepas pembedahan. Tidak terdapat perbezaan tahap kesakitan yang ketara antara dua kumpulan (30 minit, p = 0.450; 12 jam, p = 0.402; and 24 jam, p = 1.000). Penggunaan PCA morfin antara dua kumpulan pada 30 minit, 12 jam, dan 24 jam selepas pembedahan juga tidak menunjukkan perbezaan yang nyata (2.7 vs 2.4 mg, p = 0.545; 12.5 vs 9.8 mg, p = 0.154; 7.7 vs 6.4 mg, p = 0.323). Kesan sampingan magnesium sulfat terhadap tekanan darah, denyutan jantung dan tahap kesedaran juga tidak menunjukkan perbezaan yang nyata di antara kedua-dua kumpulan. Kesimpulannya, kawalan kesakitan berikutan pembedahan ginekologi dengan bius umum di kalangan pesakit yang menerima samada suntikan magnesium sulfat satu ampul (2.47 g) atau 50 mg/kg secara pre-emptif untuk pesakit-pesakit BMI <35 kg/m² adalah setara dengan kesan sampingan yang minima.

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Kata kunci: *analgesia pre-emptif, magnesium sulfat, pembedahan ginekologi, penggunaan morfin, tahap kesakitan*

ABSTRACT

This study compared the analgesic effects of pre-emptive intravenous magnesium sulphate of different dosages in patients undergoing lower abdominal gynaecological surgery. Fifty-six patients with Body Mass Index (BMI) <35 kg/m^2 who underwent lower abdominal gynaecological surgery were randomly recruited into two groups. Group I received one ampoule (2.47 g) of magnesium sulphate and Group II received 50 mg/kg magnesium sulphate (based on body weight), pre-operatively. Pain score and patient controlled analgesia (PCA) morphine requirement were compared at 30 minutes, 12 hours and 24 hours post-operatively. The pain score was comparable at all intervals between the two groups (30 minutes, p = 0.450; 12 hours, p = 0.402; and 24 hours, p = 1.000). Post-operative PCA morphine requirement was not statistically significant between the two groups at 30 minutes, 12 hours, and 24 hours (2.7 vs 2.4 mg, p = 0.545; 12.5 vs 9.8 mg, p = 0.154; 7.7 vs 6.4 mg, p = 0.323). The side-effects of magnesium sulphate on blood pressure, heart rate and sedation were not statistically significant between the two groups. In conclusion, the analgesic effects of pre-emptively administered intravenous $MgSO_4$ of 2.47 g (one ampule) was comparable to 50 mg/kg in patients with BMI less than 35 kg/m^2 following lower abdominal gynaecological surgery under general anaesthesia with negligible side effects.

Keywords: gynecologic surgical procedure, magnesium sulphate, morphine usage, pre-emptive analgesia, post-operative pain

INTRODUCTION

Optimisation of post-surgical pain is important to restore post-operative function within a minimum time frame and also to reduce the risk of progressing into chronic pain. However, severe post-operative pain remains a major issue with an estimated prevalence of 20-40%. A study comparing various surgical procedures revealed that pain scores rated by patients were found to be worse in minor procedures including laparoscopic appendicectomy, haemorrhoidectomy and cholecystectomy (Gerbershagen et al. 2013; Crombie et al. 1998). The severity of pain after surgery is contributed by the approach of surgery, site of surgery, extent of tissue lesion, nerve injury and patient's psychosocial factors. Traditionally, opioid-based analgesia is administered intra-operatively for pain relief and multimodal analgesia is subsequently introduced in order to reduce the side-effects of opioids. Drugs commonly used include non-steroidal

anti-inflammatory drugs (NSAIDs), paracetamol and local anaesthetics. The idea of pre-emptive analgesia was first introduced by Wall (1988) to reduce the severity of acute post-operative pain by blocking central sensitisation. By combining pre-emptive and multimodal analgesia, this can further lead to a better post-operative pain outcome.

The use of N-methyl-D-aspartate (NMDA) receptor antagonists such as magnesium sulphate ($MgSO_4$) and ketamine has been widely practised in pain management (Ashraf 2006). Following noxious stimuli, endogenous release of glutamate and aspartate activate the NMDA receptors leading to influx of calcium into the cells and resulting in 'wind-up' phenomenon and central sensitisation which leads to the development of acute and chronic pain (Sumihisa 2005; Colin & Steven 2018). When $MgSO_4$ is used as an adjunct to opioids, it can reduce opioid requirements and its unwanted dose-related side effects as well as improve pain scores after surgery (Bujalska-Zadrozny et al. 2017). The recommended dosage regime is a loading dose of 30-50 mg/kg followed by a maintenance continuous infusion of 6-20 mg/kg/hr till the end of surgery (Do 2013). Even after administration of a single bolus without the maintenance dose, it has been reported to provide effective post-operative analgesia (Taheri et al. 2015).

Many studies have been conducted to evaluate the analgesic effects of intravenous $MgSO_4$ on different type of surgeries. Despite the different dosages and methods of administration, studies have shown promising results that $MgSO_4$ does reduce post-operative pain and analgesic requirement (Tramer et al. 1996; Mavrommati et al. 2004; Seyhan et al. 2006; Hwang et al. 2010; Taheri et al. 2015). Pre-emptive administration of 50 mg/kg $MgSO_4$ had demonstrated a better post-operative pain profile and less post-operative analgesia requirement as compared to the placebo group in open total abdominal hysterectomy (Taheri et al. 2015). Different regimes of intravenous $MgSO_4$ using 30 mg/kg was also effective as an adjunct to peri-operative analgesia (Mavrommati et al. 2004). However, commercially prepared $MgSO_4$ comes in 2.47 g in one ampoule of 5 mL. Each 5 mL ampoule contains 10 mmol of magnesium ions and 10 mmol of sulphate ions. In this study, we compared the analgesic effects of administering one ampoule [fixed dose of $MgSO_4$ (2.47 g)] with 50 mg/kg (based on body weight) and the undesirable side effects (hypotension, bradycardia and sedation) in patients who underwent lower abdominal gynaecological surgery under general anaesthesia.

MATERIALS AND METHODS

This prospective, randomised, double-blind study was approved by the Research Committee of Department of Anaesthesiology and Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and the Medical Research and Ethics Committee, UKMMC with the approval code of FF-2018-081. Written informed consent was obtained from 56 patients

between 18-65 years of age, American Society of Anaesthesiologists (ASA) physical status I and II who were scheduled for lower abdominal gynaecological surgery via a Pfannenstiel incision which included total abdominal hysterectomy with bilateral salpingo-oophrectomy, myomectomy and ovarian cystectomy. Patients with history of previous laparotomies, known allergy to $MgSO_4$, pre-existing skeletal muscle or neurological disorders, body mass index (BMI) of more than 35 kg/m^2 or on treatment with calcium channel blockers, pregnant and lactating mothers were excluded in this study.

On the day of surgery, the patient was asked to pick a sealed envelope containing information assigning to either study group (generated randomly by Microsoft Excel software) which was unknown to the researcher. Patients in Group I received one ampule of IV $MgSO_4$ (2.47 g) while those in Group II received 50 mg/kg $MgSO_4$, both diluted in 100 mL of isotonic saline and given over 15 minutes before induction of anaesthesia by the anaesthetist in-charge in the operation theatre. Patients' electrocardiogram (ECG), blood pressure, heart rate and oxygen saturation were monitored before, during and after infusion of $MgSO_4$ and continued throughout the surgery. All patients were administered a balanced general anaesthesia without premedication with 1-2 mcg/kg fentanyl, 1-2 mg/kg propofol, and 0.6 mg/kg rocuronium. After intubation, anaesthesia was maintained with sevoflurane in oxygen:air of 50%: 50% achieving a minimum alveolar concentration (MAC) of 1.0-1.2. Patients' blood pressure, mean arterial pressure (MAP) and heart rate were recorded every 5 minutes for the first 30 minutes, and then every 30 minutes thereafter until the end of surgery. Routine analgesia of 0.1 mg/kg IV morphine was given after induction of anaesthesia to both groups of patients. Boluses of fentanyl 50 mcg were given in the event of inadequate pain control intraoperatively. Episodes of hypotension (defined as a reduction of equal or more than 20% of systolic blood pressure from baseline) or bradycardia (heart rate <60/minute) were rescued with intravenous ephedrine. Local infiltration of 2 mg/kg levo-bupivacaine 0.5% was given by the surgeon at the incision site at the end of surgery.

Post-operatively, the patients were extubated and transferred to the recovery bay for monitoring. A patient controlled analgesia device containing 1 mg/mL morphine (PCA morphine) with 1 mg morphine each bolus and a lock-out interval of 5 minutes was assigned to each patient. Patients were assessed by recovery bay nurses who were blinded to the group allocation for post-operative pain using numerical rating scale (NRS) of scale 0-10, sedation score using four-point rating scale [1=Patient is fully awake, 2=Mild (occasionally drowsy) but responded to verbal command, 3=Moderate (frequently drowsy, easily arousable) and responded to tactile stimulation, 4=Sleeping (easy to rouse) but responded to pain]. The PCA morphine usage at 30 minutes were recorded before the patients were discharged

Table 1: Demographic data and pre-operative characteristics. Values are expressed in mean ± SD and numbers (percentage)

	Group 1 (n=27)	Group II (n=25)	p value
Age (years)	45.1 ± 10.4	44.0 ± 9.5	0.721
Weight (kg)	68.3 ± 9.6	71.2 ± 9.4	0.275
Height (cm)	156.5 ± 6.2	156.2 ± 5.0	0.825
Body Mass Index (kg/m2)	27.9 ± 4.1	29.3 ± 4.4	0.258
Race			
Malay	22 (81.5)	18 (72.0)	
Chinese	4 (14.8)	5 (20.0)	0.683
Indian	1 (3.7)	2 (8.0)	
ASA			
I	18 (66.7)	16 (64.0)	0.840
II	9 (33.3)	9 (36.0)	
Operation			
TAHBSO*	21 (77.8)	18 (72.0)	
Myomectomy	3 (11.1)	4 (16.0)	0.899
Ovarian cystectomy	3 (11.1)	3 (12.0)	

*total abdominal hysterectomy and bilateral salpingo-oophrectomy

to the ward. Boluses of fentanyl 25-50 mcg were given as rescue therapy to patients who experienced severe pain while in the recovery bay. In the ward, PCA morphine was continued and oral analgesia (paracetamol 1 g 6 hourly and oral etoricoxib 120 mg daily or celecoxib 200 mg twice daily) were prescribed accordingly by the reviewing gynaecologists once patients were allowed orally. Patients' pain score, sedation score and PCA morphine usage in the ward were assessed and recorded by the Acute Pain Service nurses at 12 and 24 hours, post-operatively. Besides this, routine post-operative monitoring of blood pressure, heart rate and urine output were also performed. In this study, the researcher, patients, outcome assessors (recovery bay and ward staff nurses) were blinded to the group allocation.

The sample size calculation was done using Snedecor and Cochran (Snedecor & Cochran 1989) formula whereby it was estimated based on similar study by Hussein et al. 2016. The power of this study was set at 80%, α-value of 0.05, and a standard deviation of 4.6 for the calculation of sample size. A total of 50 patients were required for this study. Anticipating a 10% drop out, 56 patients were recruited. Data was analysed using IBM SPSS Statistics version 20.0. For numerical data, independent t-test or Mann-Whitney U test were used for the analysis of normally distributed data and not normally distributed data respectively. For categorical data, analysis was done using Chi-square test or Fisher's exact test. Repeated

Table 2: Post-operative pain assessment at various time intervals. Values are expressed in numbers (percentage).

	Group 1 (n=27)	Group II (n=25)	p value
Pain score at 30 minutes			
Mild	14 (51.9)	11 (44)	
Moderate	10 (37.0)	13 (52)	0.450
Severe	3 (11.1)	1 (4.0)	
Pain score at 12 hours			
Mild	17 (63.0)	12 (48.0)	0.402
Moderate	10 (37.0)	13 (52.0)	
Pain score at 24 hours			
Mild	24 (88.9)	23 (92.0)	1.000
Moderate	3 (11.1)	2 (8.0)	

measures ANOVA was used to analyse haemodynamic data over time. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 56 patients were recruited into this study. However, four patients (one in Group I and three in Group II) dropped out due to conversion of Pfannenstiel incision to midline above umbilicus incision, intra-operatively. Demographic data and pre-operative characteristics of patients were comparable in both groups and are shown in Table 1.

Pain assessment using NRS was further categorised into mild (1-3), moderate (4-6) and severe (7-10). None of the patients experienced severe pain at 12 and 24 hours after surgery. Table 2 showed that pain score at all time intervals were comparable between the two groups. Sedation score was assessed using four-point rating scale. Majority of patients were fully awake at 12 hours and all were fully awake by 24 hours post-surgery (Table 3). PCA morphine usage post-operatively

Table 3: Post-operative sedation score. Values are expressed in numbers (percentage)

	Group 1 (n=27)	Group II (n=25)	p value
Sedation at 30 minutes			
Fully awake	13 (48.1)	13 (52.0)	
Mildly sedated	14 (51.9)	9 (36.0)	0.160
Moderately sedated	0 (0.0)	3 (12.0)	
Sedation at 12 hours			
Fully awake	26 (96.3)	23 (92.0)	0.603
Mildly sedated	1 (3.7)	2 (8.0)	

Table 4: Post-operative PCA morphine (mg) usage over various time intervals. Values are expressed in mean ±SD

	Group 1 (n=27)	Group II (n=25)	p value
30 minutes	2.7 ± 1.9	2.4 ± 1.6	0.545
12 hours	12.5 ± 7.5	9.8 ± 6.0	0.154
24 hours	7.7 ± 4.6	6.4 ± 4.2	0.323

for both groups at 30 minutes, 12 hours, and 24 hours demonstrated no significant differences as shown in Table 4.

Serial readings of mean arterial pressure (MAP) and heart rate were recorded prior to administration of $MgSO_4$ up to 60 minutes intra-operatively. The MAP and heart rate at each time interval were comparable between the two groups (p>0.05). The lowest mean recorded for MAP in Group II was 75.9±10.7 mmHg at 10 minutes after induction and the lowest mean heart rate was 70.2±14.3 bpm at 30 minutes after induction in Group II (Figures 1 & 2). None of the patients experienced hypotension, bradycardia and muscle weakness over the first 24 hours, post-operatively.

DISCUSSION

Administration of $MgSO_4$ before the generation of noxious surgical stimulus can prevent central sensitisation thereby reducing acute post-operative pain. This study was done to compare the pre-emptive analgesic effects of administering one ampoule $MgSO_4$ (2.47 g) versus 50 mg/kg $MgSO_4$ (calculated based on body weight) and the results showed that the pain score and analgesia requirement post-operatively were comparable between the two dosages in our patients who underwent lower abdominal gynaecological surgery during the first 24 hours. The mean weight of patients in Group I was 68.3±9.6 kg. Thus, the average dosage received by patients in Group I who received one ampoule of

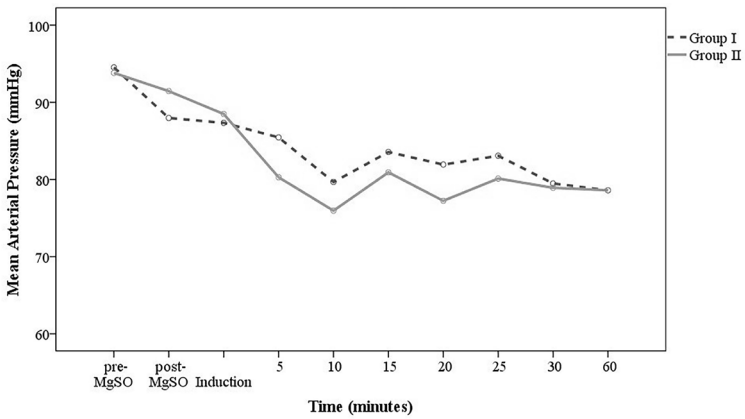

Figure 1: Perioperative changes in mean arterial pressure (mmHg)

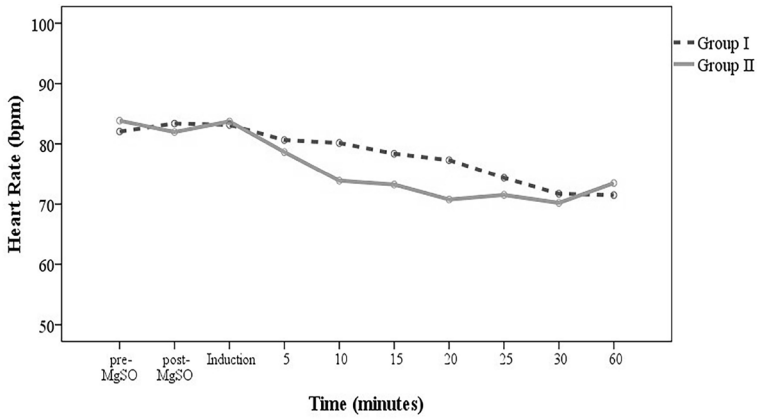

Figure 2: Perioperative changes in heart rate (bpm)

$MgSO_4$ of 2.47 g was 36 mg/kg which was within the recommended dose. In our cohort of patients, majority of them experienced mild to moderate pain at 30 minutes and 12 hours post-operatively and PCA morphine demands during these periods were similar in both groups. Only a small number of them [3 (11.1%) vs 1 (4.0 %), p=0.450] experienced severe pain which required rescue bolus doses of fentanyl 25-50 mcg before being discharged back to the ward (Table 2). This finding was consistent with a previous study which showed that administering a lower dose at 30 mg/kg of $MgSO_4$ bolus before the start of surgery followed by an infusion of 6 mg/kg/hour over the entire operation period compared to the control group (normal saline) was an effective analgesic adjunct in patients who underwent abdominal hernioplasty whereby fentanyl consumption intra and post-operatively was significantly less in the magnesium group (Mavrommati et al. 2004). Similarly, Helmy et al. (2015) showed that $MgSO_4$ at 30 mg/kg administered 10 minutes before induction of anaesthesia was found to significantly reduce intra-operative fentanyl requirement compared to the control (normal saline) group in Prturients undergoing Caesarean section.

Pain after gynaecological surgery can be due to incision site or from deeper visceral structures especially during movement, straining or coughing and this visceral pain can dominate up to the first 48 hours after hysterectomy (Leung et al. 2000). However, most of the investigators in previous similar studies only monitored the analgesic effects up to 24 hours post-surgery (Kiran et al. 2011; Kaur & Baghla 2012; Taheri et al. 2015; Vasupalli & Prakash 2016). For the purpose of this study, we monitored the pain score up to the first 24 hours and majority of our patients from both groups experienced only mild pain at 24 hours post-operatively (88.9 vs 92.0%, p=1.000) with a concurrent reduction in PCA morphine demand (7.7$\pm$4.6 vs 6.4$\pm$4.2 mg, p=0.323) during this period. This clearly showed that the analgesic effects of $MgSO_4$ at a dose of 2.47 g

(36 mg/kg) was as effective as 50 mg/kg.

$MgSO_4$ prevents catecholamine release and therefore results in bradycardia and vasodilation. With the doses used in this study, the adverse effects of $MgSO_4$ on blood pressure and heart rate were negligible, consistent with previous studies (Kaur & Baghla 2012; Ryu et al. 2008; Mavrommati et al. 2004). Even though the lowest mean recorded values for both MAP and heart rate were from Group II, the values were still within normal acceptable range (Figures 1 & 2). Both dosages were safe and effective for patients with normal body weight to Class I obesity (mean BMI were 27.9 ± 4.1 and 29.3 ± 4.4 kg/m^2 in Groups I and II, respectively).

Magnesium sulphate is a relatively safe drug with high therapeutic index. The normal plasma concentration of magnesium ranges between 0.7-1.3 mmol/L. Magnesium toxicity occurs when the levels exceed 4 mmol/L with a loss of deep tendon reflex and drowsiness and may result in cardiac arrest when the levels reach 8 mmol/L (Fawcett et al. 1999). Serum magnesium level was however not measured and patellar reflexes were also not assessed in this study as previous studies have repeatedly shown that the level of magnesium in the blood were below toxic levels with the dosages administered. Moreover, our cohort of patients do not have impaired renal function which may impair the clearance and excretion of magnesium leading to toxicity. The maximum measured serum magnesium concentrations were in the range of 1.31 to 1.50 mmol/L, despite having received 50 mg/kg bolus and 15 mg/kg/hour infusion of $MgSO_4$ intra-operatively (Hwang et al. 2010, Na et al. 2010; Ryu et al. 2008; Tramer et al. 1996) which was still within the normal therapeutic range.

Magnesium decreases release of acetylcholine at the presynaptic nerve terminals which diminishes the excitability of skeletal muscle fibres and reduces the endplate potential amplitude, resulting in the potentiation of neuromuscular blockade by nondepolarising muscle relaxants (Ryu et al. 2008). Rocuronium, a nondepolarising muscle relaxant was used in our cohort of patients for the purpose of intubation as well as providing optimum operating conditions for the surgeons. Despite the potentiating effects exerted by $MgSO_4$, our patients from both groups did not experience any delay from recovery of general anaesthesia or any residual muscle weakness in the recovery bay of the operating theatre which required an additional dose of anticholinesterase (neostigmine). This could be due to the dose of $MgSO_4$ administered which was within the normal recommended dosage and also the pre-operative normal renal function of our patients which are required in the clearance of $MgSO_4$ as well as rocuronium.

The present study demonstrated that by infusing a single ampule $MgSO_4$ (2.47 g), the pain control and analgesia requirement was comparable to that of 50 mg/kg after gynaecological surgery for the first 24 hours. Therefore, by using a single ampule of $MgSO_4$,

unnecessary wastage of $MgSO_4$ can be avoided. This however only applies to patients with BMI 35 kg/m^2 and below who were the subjects in this study. The analgesic effects and related side effects for morbidly obese patients was not studied.

CONCLUSION

The analgesic effects of pre-emptively administered intravenous $MgSO_4$ of 2.47 g (one ampule) was comparable to 50 mg/kg in patients with BMI less than 35 kg/m^2 following gynaecological surgery under general anaesthesia with negligible side effects.

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