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ORIGINAL RESEARCH GENERAL ANESTHESIA

Comparison of the effect of magnesium sulfate 50 mg/kg with 30 mg/kg on opioid requirement and blood magnesium level after abdominal hysterectomy

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ABSTRACT

Background: Hysterectomy is the most common operation with a postoperative pain score for abdominal hysterectomy being 8. Preemptive analgesia can help mitigate the postoperative pain. We studied the effect of preoperative use of magnesium sulfate ($MgSO_4$), either in a dose of 50 mg/kg or 30 mg/kg, on the opioid requirements as well as on the serum magnesium levels in abdominal hysterectomy patients.

Methodology: This was a double-blind, randomized controlled, clinical trial with 40 women undergoing abdominal hysterectomy included as participants. The participants were randomly divided into two groups; Group I received $MgSO_4$ 30 mg/kg and Group II received a dose of 50 mg/kg, 20 min before induction of routine general anesthesia. Pre-operative and postoperative blood magnesium levels were compared by unpaired t-test. Inter-group comparison was also done.

Results: Group I patients had lower postoperative opioid requirements compared to the Group II. There was a significant difference in blood magnesium levels between the two groups; e.g., 2.36 ± 0.29 vs.2.13 ± 0.23 mEq/L in Group I and Group II, respectively.

Conclusion: Administering magnesium sulfate at a dose of 50 mg/kg to abdominal hysterectomy patients can reduce the need for opioids and significantly increase the magnesium levels in the blood compared to a dose of 30 mg/kg.

Keywords: Abdominal hysterectomy; Magnesium sulfate; Opioid; Preemptive analgesia

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1. INTRODUCTION

Preemptive analgesia is an initiation therapy given before and at the time of a surgical procedure aimed at reducing the physiological side effects of nociceptive transmission provoked by surgery. Preemptive analgesia has the potential to be more effective than similar analgesia initiation therapies administered postoperatively so that rapidly arising postoperative pain can be reduced and prevent pain from becoming chronic. Preemptive analgesia can be administered via local, epidural, or systemic wound infiltration. Studies conducted on patients given preemptive analgesia concluded that patients experienced decreased requirement of postoperative analgesia.[1-5] Postoperative pain is considered a form of acute pain due to surgical trauma accompanied by an inflammatory reaction and stimulation of afferent neuronal circuits. Postoperative pain is a problem for the patients and a challenge for the

anesthesiologists and surgeons. The incidence of moderate to severe pain varies globally, in western countries there is a 14% to 55% incidence, the highest on the day of surgery. In low to middle-income countries, the prevalence can increase up to 95% in Kenya and Ethiopia based on cohort studies. A study on the prevalence of postoperative pain conducted at Kilimanjaro Christian Medical Center, Tanzania showed that about 73% of patients experienced moderate to severe pain on the first postoperative day.[6-7] Eight studies comparing the administration of various types of opioids during hysterectomies, preoperatively and postoperatively, revealed no significant decrease in pain scores in the preemptive group. In contrast, a quantitative study found that there was no increase in the use of postoperative analgesia after preemptive therapy with intravenous opioids. Twenty meta-analyses on various types of odontology, abdominal, and orthopedic surgical procedures concluded that there was no advantage in using NSAIDs as preemptive therapy compared to postoperative NSAID administration.[3-5,8-9]

Most of the analgesia regimens used for postoperative pain management comprise of opioids. Several medication protocols besides opioids, have been used. The most commonly used opioids are morphine, hydromorphone, and fentanyl. However, the use of opioids has significant side effects that limit their use. The most common side effects are airway depression, nausea, vomiting, pruritus, and decreased intestinal motility which results in ileus and constipation. Prolonged use of opioids can lead to addiction.[1-2]

N-methyl-D-aspartate receptor antagonists (NMDA) are one type of drugs used of preemptive analgesia. Some studies conducted on dextromethorphan produced positive results, but the sample size used was too small to produce definitive conclusions. In preemptive therapy using epidural, caudal, and spinal regimens, no effective results were found in 4 out of 5 studies. The results of a meta-analysis comparing preemptive analgesia with continuous epidural analgesia showed no improvement in postoperative pain.

The authors compared use of preoperative magnesium sulfate 50 mg/kg with 30 mg/kg on opioid requirements and blood magnesium levels after abdominal hysterectomy.

2. METHODOLOGY

A double-blind randomized control trial was conducted in Hasan Sadikin General Hospital, Bandung, Indonesia, from July to October 2023. We used a randomized sampling technique, and the allocation of subjects into one of the groups was done by randomized block permutation. Sample size was determined using the independent-continuous variable sample size formula (2-group unpaired comparative analytics with 95% confidence interval, Zα 1.64, and Zβ 1.28) with 20 subjects for each group. Patients aged 20-60 y with ASA physical status I-II and junior high school or equivalent as the last education status, were included. A previous research showed that last educational status is a major factor in the interpretation of pain. Those with preoperative serum magnesium levels less than 1.8 mg/dl or more than 2.4 mg/dl, patients on calcium channel blocking agents, or those with a history of allergy to drugs used in this study were excluded. The drop-out criteria were; an operation length of more than 4 h because the average duration of abdominal hysterectomy operation in our institution is 4 h.

The research team carried out randomization using permuted blocks so that they found which individuals would fall into Group I and Group II. The research team gave instructions to the pharmacy team to determine patients according to the sequence of randomization that had been carried out previously. The pharmacy team compounded the magnesium sulfate ($MgSO_4$) solution. The anesthesiologist in charge administered $MgSO_4$ solution and carried out intraoperative monitoring according to the research flow.

All patients were given premedication with lorazepam 0.02 mg/kg orally 8 h before surgery. The patients were transferred to the operating room and then non-invasively monitored for blood pressure, electrocardiography, pulse rate, respiratory rate, and oxygen saturation. Group I was given a 20% MgSO4 solution, which had been dissolved in 0.9% NaCl to make 50 ml with a dose of 30 mg/kg infused 20 min before induction using a syringe pump. Group II received a 20% MgSO4 solution which had been dissolved in 0.9% NaCl to make 50 ml with a dose of 50 mg/kg given over 20 min before induction using a syringe pump.

Twenty minutes after administering IV $MgSO_4$, induction of anesthesia was carried out with fentanyl 2 µg/kg, propofol 2 mg/kg, and atracurium 0.5 mg/kg. Maintenance of anesthesia was done with sevoflurane, N_2O, and O_2. Administration of 0.5 µg/kg IV fentanyl was carried out if signs of an increase in pulse rate or blood pressure of more than 20% are found. The nerve stimulator was placed on the ulnar side of the forearm and administered with supramaximal stimulation at 10-min intervals. Hemodynamic parameters, diuresis, side effects and duration of the surgical procedure were recorded. When the skin was sutured, a blood sample was taken for post-operative serum magnesium level examination. Neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were given at the end of the operation. Ketorolac 0.5 mg/kg bolus was given at the time of skin closure and

Table 1: Demographic data of the participants

Characteristics	Group I (n = 20)	Group II (n = 20)	P
Age (y)	42,05 ± 6,40	41,00 ± 7,42	0.635
ASA status			
• 1	12 (54.50)	10 (45.50)	0.525
• 2	8 (44.40)	10 (55.60)	
Education status			
• Elementary school	12 (60.0 0)	8 (40.0 0)	0.206
• High school	8 (40.0 0)	12 (60.0 0)	
Body weight (kg)	57.00 (52-64)	57.00 (52-62)	0.718
Data presented as mean ± SD or n (%); P < 0.05 considered as significant			

Table 2: Comparative surgery duration opioid requirement

Variable	Group I (n = 20)	Group II (n = 20)	P
Surgery duration (min)	190.25 ± 20.49	184.50 ± 14.23	0.310
Intraoperative opioid use (µg)	66.00 ± 15.35	60.0 0 ± 17.61	0.098
Postoperative analgesic use in 24 h (µg)	525.00 (500-600)	362.50 (275-400)	< 0.001*
Data presented as mean ± SD or n (range); P < 0.05 considered as significant			

inhalation gas was stopped. Patients were extubated when fully responding to verbal commands and transferred to the recovery room.

For postoperative analgesia we used IV fentanyl through PCA pump. The pump was set to provide a bolus dose of 25 µg on demand with a lockout period of 10 min without setting a continuous basal infusion dose with a maximum dose of 10 µg/kg/day and recording of the total amount of fentanyl in 24 h.

Data were entered in SPSS vs. 24, and was analyzed by unpaired t-test.

3. RESULTS

The study was conducted on 40 patients who underwent abdominal hysterectomy surgery under general anesthesia at a tertiary hospital in West Java, Indonesia. Four patients were excluded because the duration of operation was more than 4 h. An overview of the demographic characteristics of the research subjects is shown in Table 1. The results of statistical analysis showed that the characteristics of the two groups were the equivalent, with no differences in characteristics (P > 0.05).

Postoperatively total amount of fentanyl administered during the first 24 h using PCA IV was analyzed by unpaired t-test. The comparison of surgery duration, intraoperative opioid use and postoperative total opioid used within 24 h postoperatively between both groups is shown in Table 3.

Examination of blood magnesium levels was performed two times, the first one a day before the operation (called as pre-operative blood magnesium levels) and the second, when the surgeon started subcutaneous sutures (called as post-operative blood magnesium levels). Pre-operative blood magnesium levels were analyzed by unpaired t-test. The comparison of preoperative and postoperative blood magnesium levels between both groups is shown in Table 3. There was no significant difference (P = 0.758) in preoperative blood magnesium levels between Group I and Group II. Postoperative blood magnesium levels were analyzed by unpaired t-test and found to be higher in Group II than Group I and had a significant difference with a P = 0.002.

Examination of the pain scale based on the numeric rating scale (NRS) was carried out after one hour, 12 h, and 24 h postoperatively, then analyzed with generalized linear model (GLM): repeated measures. The comparison of the pain scale between both groups is shown in Table 4. The pain scale was found to be lower in Group II than Group I at 1 hour postoperatively (mean 5 compared to 8), 12 h postoperatively (mean 4

Table 3: Preoperative and postoperative blood magnesium levels

Variable	Magnesium Level (mEq/L)		Test	P-value
	Group I (n = 20)	Group II (n = 20)		
Preoperative sample	2.05 (1.8-2.4)	2.10 (1.8-2.2)	Unpaired t-test	0.758
Postoperative sample	2.13 ± 0.23	2.36 ± 0.29		0.0 02*

Data presented as mean ± SD or n (range); P < 0.05 considered as significant

compared to 5.5), and both results were found to be lower and statistically significant (P < 0,001). At 24 h postoperative, the results with Group II were found to be lower than Group I (mean 2 compared to 3) but the results were not statistically significantly different (P = 0,277).

Regarding the side effects found due to IV $MgSO_4$ administration, pain during injection was found in 3 patients in Group II. Other side effects such as warmth or heat in the face, redness, nausea and vomiting, muscle weakness, drowsiness, headache, hypotension, bradycardia, and sedation were not reported by any of the patients.

Table 4: Patient pain score based on numeric rating scale (NRS)

Time	Numeric Rating Scale		P-value
	Group I (n = 20)	Group II (n = 20)	
Hour-1	8 (6-9)	5 (4-8)	< 0.001*
Hour-12	5.5 (5-7)	4 (3-5)	< 0.001*
Hour-24	3 (1-4)	2 (1-3)	0.277*

Data presented as number (range); P < 0.05 considered as significant

4. DISCUSSION

Postoperative pain is a problem that is still a concern in the world because it can cause various side effects, both physically and psychologically from postoperative patients, so adequate analgesia is needed as one of the medical therapies, including NSAID and opioids. Narcotics such as fentanyl are widely used and are cost-effective agents in postoperative pain control. However, the therapeutic side effects associated with their use are a concern. Finding a safe and cost-effective method for pain control is still a matter of medical debate. Several studies have evaluated the role of an NMDA receptor antagonist, $MgSO_4$, as an analgesic. Some studies conclude that $MgSO_4$ can reduce postoperative opioid requirements., such as $MgSO_4$, have the effect of increasing the pain threshold and can prevent pain perception even with low-dose administration. A study compared the use of 50 mg/kg $MgSO_4$ 0.9% sodium chloride fluid 15 min before induction under GA. The study concluded that a preventive dose of $MgSO_4$ can reduce first-day postoperative pain scores and was reported without any side effects such as nausea, vomiting, hypotension, or hypermagnesemia.[5,8] Another double-blind study in 30 women concluded that $MgSO_4$ during surgery reduced postoperative pain.[8] Intravenous $MgSO_4$ given as a bolus before induction is expected to have an effect by reducing the use of postoperative analgesia due to its non-competitive NMDA receptor antagonist properties. The dose of $MgSO_4$ that can be used ranges from 30-50 mg/kg with or without a maintenance dose. [3-5,9] Hysterectomy is the most commonly performed gynecologic surgery that leads to prolonged length of stay due to postoperative pain experienced by the patient, thus reducing the patient's quality of life. In patients with abdominal hysterectomies, the pain measurement based on the Visual Analog Scale (VAS) score.[5-8.10-13]

The use of opioid analgesia has side effects that need to be considered. Intravenous $MgSO_4$ given as a bolus before induction is expected to have an effect by reducing the need of postoperative analgesia due to its non-competitive NMDA receptor antagonist properties. The dose of $MgSO_4$ ranges from 30-50 mg/kg with or without a maintenance dose.

In our study, the need for analgesics within 24 h postoperatively was found to be significantly lower in Group II compared to the Group-I (P < 0.001). The results of this study are in accordance with research conducted previously.[14] A meta-analysis study concluded that administration of $MgSO_4$ IV between 40 - 50 mg/kg before induction, without the administration intraoperatively, can reduce the need for postoperative opioids but it cannot be sure whether other doses of $MgSO_4$ IV before induction can have the same outcome or not.[15]

Another study on 42 patients undergoing abdominal hysterectomy concluded that the administration of 15 ml of 20% $MgSO_4$ can reduce morphine requirement by 26 mg compared to the control within 12 h postoperatively.

A double-blind randomized study on 100 male patients, who underwent open prostatectomy, found that the administration of $MgSO_4$ 50 mg/kg 20 min before induction can reduce the need for tramadol PCA as postoperative analgesia by 21 mg. This study also found that the time first analgesic was 2.7 h faster in the control compared to the $MgSO_4$ group.[15,16.]

Research on the administration of a maintenance dose has been carried out previously in the Department of Anesthesiology and Intensive Therapy Department, Faculty of Medicine, Padjadjaran University, in gynecologic abdominal surgery. This study showed that the administration of $MgSO_4$ 50 mg/kg 15 min before induction and continued with infusion of 10 mg/kg/h decreased the need for pethidine by 2.95 mg in the $MgSO_4$ group compared to the control group. Other studies have proven $MgSO_4$ infusion did not give a better effect than compared to the administration of a single bolus dose before induction.[17,18.]

In our study, postoperative opioid requirement was found to be higher in the research subjects in Group I compared to Group II; a statistically significant difference. In this study there was no significant difference in the length of surgery between the two groups. Postoperative pain of abdominal hysterectomy is also influenced by the history of surgery in patients who have undergone laparotomy earlier. Other factors such as social culture, subjectivity, understanding of pain cannot be ruled out in this study.[19]

We used a fentanyl PCA pump postoperatively. Fentanyl can be used as postoperative analgesia using a PCA pump.[20]

The magnesium levels in blood were found to be significantly higher in Group II with a mean of 2.36 ± 0.29 vs 2.13 ± 0.23 mEq/L ($P = 0.002$) in Group I. This level is still within the safe limits, so no side effects occurred. Serum magnesium 5 to 7 mg/dL gives symptoms in the form of lethargy, nausea, vomiting, and loss of tendon reflexes. Magnesium levels of 7 to 12 mg/dL manifest as hypotension and electrocardiographic changes. At levels < 2 mg/dL can cause coma, paralysis, apnea, and cardiac conduction block.[19]

A previous study in 24 patients who were given $MgSO_4$ IV 30 mg/kg before induction and given a 500 mg/h maintenance for 20 h postoperatively explained that at 20th h postoperatively, patients from the control group had significantly lower serum magnesium concentrations compared to the value before treatment with a value of $P < 0.05$ which means that there is a significant difference. $MgSO_4$ IV has been used for a long time in obstetric and cardiovascular practice, but its role as preemptive analgesia, especially in abdominal hysterectomy is still debated.[22]

Adverse side effects of $MgSO_4$ from causing reluctance to use $MgSO_4$ without availability of its antidote calcium gluconate or examination of magnesium levels in the blood. Some factors that influence the effects of $MgSO_4$ include the dose and mode of administration, total fluid, total bleeding during surgery, serum magnesium levels, and duration of surgery. In this study, postoperative serum magnesium levels were still within normal limits.

Hypotension due to administration of $MgSO_4$ occurs due to calcium channel blockade so that vasodilation occurs. This situation rarely occurs in the administration of $MgSO_4$ up to a dose of 60 mg/kg.[8]

Administration of $MgSO_4$ IV 50 mg/kg before induction showed side effects of nausea in two patients. Research on 42 patients showed no hypotensive side effects were found due to $MgSO_4$ administration. In another study, although hypotension occurred in 8 patients in the group who were given $MgSO_4$, but this also occurred in 6 patients in the control group. The side effect of prolonging the duration of action of muscle paralyzers extended by 20.8 min compared to the control and was found in other studies.[16]

NRS pain scores were registered at 1 h ($P < 0.001$) and 12 h ($P < 0.001$) postoperatively. Group II was significantly lower than Group I. While at 24 h postoperatively, the results of the pain scale with Group II where group was found to be lower than Group I (mean 2 compared to 3) but these results were not statistically significant ($P = 0.277$). This is in line with research conducted by Jarahzadeh et al. which showed that the administration of $MgSO_4$ 50 mg/kg can reduce pain scores at 1 hour and 12 h postoperative hysterectomy compared to the control group.[23]

In accordance with studies that measure pain scale using NRS, obtained at 12 h and 24 h postoperative, pain scores in the group given $MgSO_4$ 50 mg/kg were lower than the control group.[24] Meanwhile, in a study comparing the difference in dosing of $MgSO_4$ against postoperative pain in the first 24 h, it was found that giving $MgSO_4$ with a larger dose can reduce the mean NRS lower than the control group ($P < 0.05$).[25]

Postoperative pain and its possible mechanisms include two main components: inflammation and neuropathy. Both components are characterized by increased sensitivity and response to pain. Pain due to this inflammatory response is caused by the release of substance P and calcitonin-associated peptides from primary afferent neurons as well as the release of prostaglandins. So that there is peripheral sensitization or increased sensitivity to pain stimuli, lowering the pain threshold, and enhancing the response to to tissues that are experiencing inflammation. Meanwhile, neuropathic pain occurs due to damage to the afferent nerves because of surgery which can occur postoperatively. This

neuropathic pain can also occur due to changes in ionic activity and the release of proinflammatory factors. These factors will interact with nerve fibers and result in increased input to the central nervous system causing sensitization to the central nervous system leading to central sensitization.

5.LIMITATIONS

The limitation of this research is the small population size and further research is needed on the use of $MgSO_4$ IV bolus by expanding the study to include various types of surgery other than abdominal hysterectomy. We need to determine the effectiveness of $MgSO_4$ administration on other clinical outcomes too, such as length of hospital stay and quality of postoperative recovery.

6. CONCLUSIONS

Administration of $MgSO_4$ IV bolus dose of 50 mg/kg before induction proved to reduce postoperative opioid requirements more than the dose of 30 mg/kg in abdominal hysterectomy surgery. Postoperative blood magnesium levels in the administration of $MgSO_4$ IV bolus dose of 50 mg/kg before induction were higher than the dose of 30 mg/kg. Administration of a larger dose caused pain during injection, but it showed lower postoperative pain scores compared to the administration of 30 mg/kg.

Based on the results of this study, it can be recommended to administer $MgSO_4$ IV bolus dose of 50 mg/kg in patients who will undergo abdominal hysterectomy to reduce the need for postoperative opioids.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

All authors took equal part in the concept, conduct of the study, compilation of the data, statistical analysis and drafting and editing the manuscript.

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