ORIGINAL ARTICLE

Effects of Intravenous Magnesium-Sulphate on Postoperative Analgesia following Myomectomies and Hysterectomies

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ABSTRACT **Background:** Opioids are the mainstay of postoperative analgesic, but with many side effects. We explored the analgesic effects of magnesium preloading in abdominal surgeries.
Methodology: Eighty patients, 18 – 65 years, ASA I-III, were randomised into groups M and N. Prior to induction of general anaesthesia, group M received IV magnesium 50mg/kg preloading while group N received placebo, both in 100mls 0.9% saline over 15 mins. All patients had paracetamol 1gm, pethidine 0.5mg/kg and wound infiltration. The time to first request for rescue IV pentazocine, total rescue opioid use, postoperative VAS pain scores over 24-hours, side effects profile and satisfaction score were compared.
Results: Demographic parameters were comparable, p-value > 0.05. The mean time to first request for rescue analgesia was prolonged in group M (219.25 ± 148.88 mins) compared to group N (82.25 ± 46.51 mins). The mean postoperative VAS pain scores were lower in group M versus group N over 24-hours ($p < 0.05$). The mean 24-hours rescue opioid use was lower in group M (49.23 ± 20.05mg) versus group N (87.00 ± 15.27mg), p-value 0.001. PONV was lower in group M versus N, p-value 0.001. Group M had better satisfaction score versus N, p-value 0.001.
Conclusion: Magnesium 50mg/kg preloading provided effective postoperative analgesia, and lower rescue opioid use and PONV incidence following gynaecological surgeries.
Keywords: Magnesium Sulphate, Pain, Opioids, Myomectomy, Hysterectomy.

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INTRODUCTION

Postoperative pain is a significant surgical concern for patients, especially in low-resource countries (LRCs), where analgesic options are limited.[1,2] For instance, the incidence of moderate to severe pain following caesarean section (CS) in Nigeria is between 54.6 - 79.6%.[1] Another African study reported a moderate to severe pain incidence 73.1% after gynaecological procedures.[3] The fear of pain and death are the commonest concerns in Nigerian surgical patients.[4]

The problem of inadequate postoperative analgesia is far reaching. These includes myocardial ischaemia, arrythmias, hypoventilation, atelectasis, hypoxia, postoperative delirium, thromboembolism, and hyperglycemia. Also, it delays recovery, prolong hospital stay and its attendant economic consequences.[2]

The current approach to postoperative analgesia is multimodal. It employs the use of more than one drug, mechanism, and techniques to target several sites in the pain pathway.[5]

Opioids such as morphine, fentanyl, alfentanil and pethidine form the cornerstone of multimodal analgesia, owing to their potent analgesic effects. However, the draw-backs are sedation, ventilatory depression,

vomiting, constipation, urinary retention and urethral catheterization. These problems add to patient's morbidity. Thus, there is a need to explore agents that can lower opioids requirements, and consequently its side effects.[6]

Several agents have been explored i.e., muscle relaxants e.g., gabapentin, antidepressant e.g., amitriptyline, benzodiazepines e.g., midazolam, and alpha-agonists e.g., dexmedetomidine, with mixed outcomes.[2,5,6]

Magnesium is increasingly used in anaesthesia due to its anti-convulsant, anti-inflammatory, and modulatory properties. It stabilise cell membrane, via the blockade of N-methyl-D-Aspartate (NMDA) receptor and calcium ion cellular influx. It modulates pain pathway, and promotes neuronal hyperpolarisation, thus precluding pain intensity.[7] It lowers postoperative pain severity after laparoscopies,[8] abdominal surgeries,[9] hysterectomies,[10,11] and spine surgeries.[12] We noted that magnesium's analgesic property is rarely studied in sub-Saharan African population, where variations in physiology, genetics, and surgical settings may influence its efficacy and safety.

This study aimed to investigate the effect of intravenous (IV) magnesium 50mg/kg preloading, on the time to first request for rescue analgesic, postoperative VAS pain scores, total rescue analgesic consumed, PONV incidence, and satisfaction score in women undergoing hysterectomies or myomectomies, at Ile-Ife, Nigeria.

PATIENTS AND METHOD

This prospective, randomised controlled study was conducted between October 2021 and April 2022. Approval was obtained from Ethics committee of Obafemi Awolowo University Teaching Hospitals complex (OAUTHC), Ile-Ife, Nigeria, protocol No: ERC 2021/03/06.

Women, aged 18 – 65 years, with ASA status I, II and III scheduled for myomectomies and hysterectomies were included. Consent refusal, cyesis, obesity, severe heart, lung, and liver disease, allergy to study drug, malignancy, and behavioral illness were exclusion criteria.

The minimum sample size was on the mean on two non-dependent variables, using Kirkwood formula,[13] based on the time to first request for rescue analgesia

$$n = \frac{(u + v)^2 (SD1^2 + SD2^2)}{(U1 - U2)^2}$$

$$= \frac{(1.28 + 1.96)^2 (140.1^2 + 93.34^2)}{(90.61)} = 36.7$$

Adding 10% attrition = 40 per group. Thus, a total of 80 patients were studied.

A statistician used a computer-generated table to prepare random numbers, written on leveled cards, stored in an envelope, and un-coded after the study. For each patient, the pharmacist was informed, who prepare the study drugs. Thus, the anaesthetist and patients were blinded. The Anaesthestist gave the anaesthesia, and recorded all data. Group M received 50mg/kg magnesium (AS Kalceks) while group N patients received saline 0.9%.

Patients were recruited a day to surgery. History, examination and investigations, i.e., full blood count, electrolytes, coagulation, 12-lead electrocardiograph (ECG), and chest imaging were reviewed. Informed consent was taken.

On the morning of surgery, the anaesthesia machine was checked. Patients baseline pulse rate (PR), blood pressure (BP), saturation (SPO_2), and 5-lead ECG tracing were recorded. IV access was secured and 0.9% saline 500ml commenced. Ondansetron 4mg and dexamethasone 8mg were given. Just before induction, 100mls of the study drugs were infused over 15mins.

Patients were preoxygenated with 100% oxygen for 2 – 3 mins. Induction was done with propofol 1.5 – 2mg/kg. Succinylcholine 1.5mg/kg was administered. Tracheal intubation was done with endotracheal tube (ETT) 7.0mm, confirmed with capnography, connected to the Anaesthetic machine via circle system, and maintained with 0.8 – 1.5% isoflurane in oxygen. Ventilation was controlled mechanically. Muscle paralysis was maintained with vecuronium 0.lmg/kg, as required. Paracetamol 1gm and pethidine 0.5mg/kg was given. Stable haemodynamic, normocapnia, normoxia, and normothermia were maintained.

After the surgery, the wound site was infiltrated with 40mls of 0.25% plain bupivacaine. Isoflurane was turned off, residual paralysis reversed with neostigmine 0.05mg/kg and atropine 0.02mg/kg, airway suctioned, extubated and given 100% oxygen by facemask. Afterwards, the patient was transferred to the recovery room for monitoring, and discharged to the ward using modified Aldrete score of at least 9. IM diclofenac 75mg 12 hourly and paracetamol 1gm 8 hourly were given for 48-hours.

The postoperative VAS pain scores were assessed at 0-, 1-, 2-, 4-, 8-, 12-, and 24-hours. Rescue analgesic (IV pentazocine 0.5mg/kg) was given if in pain, or VAS pain score was above 3, and recorded. Drugs side effects and satisfaction score was recorded after 24-hours.

Data Analysis: Data were analysed using SPSS 25.0. Student's t-test summarised categorical data e.g., VAS pain scores as mean and standard deviation. Chi-square test summarised continuous data e.g., ASA status as frequencies and percentages. P-value < 0.05 was significant.

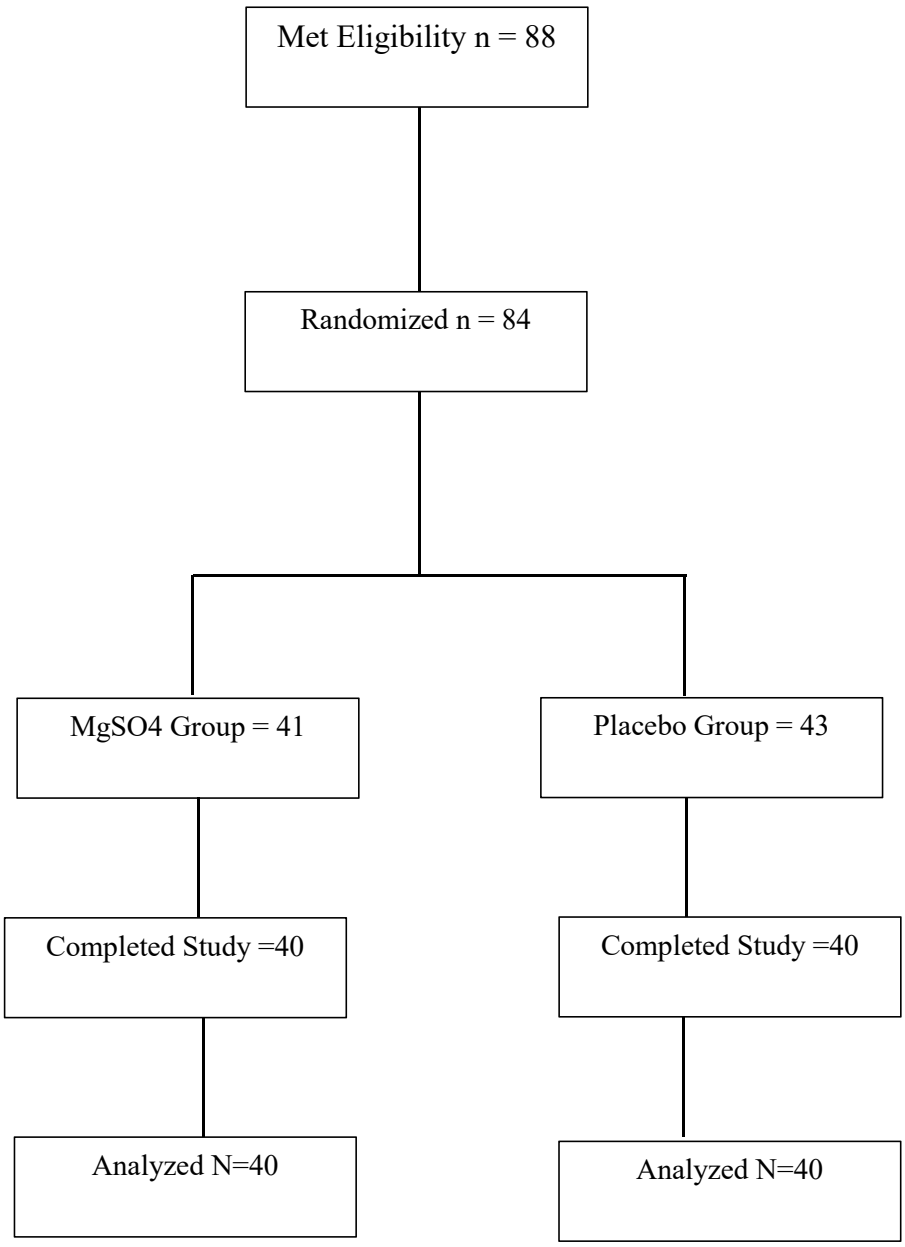

Figure 1: Flowchart Diagram

RESULTS

Eighty patients concluded the study (Figure 1). Demographics, i.e., age, weight, height, BMI, ASA, and duration of surgery were comparable, p-value of 0.80, 0.30, 0.51, 0.49 and 0.74 respectively. The baseline mean serum magnesium was similar, p-value- 0.32 (Table I). The time to first request for rescue analgesic in 219.25 ± 148.88mins group M, was statistically longer than 82.25 ± 46.51mins in group N, p- 0.001. The mean total rescue pentazocine consumed was 25.45 ± 10.75mg Group M which is less than 55.50 ± 15.25mg in Group N, p- value 0.001. The total number of patients who requested rescue doses was 8 (20%) in group M which is lower than 18 (45%) in group N p-value 0.001. (Table II). The mean VAS pain scores were lower in group M versus N at -0, -1, -2, -8, -12 and 24-hours, p-value 0.001 at each hour (Table III). PONV incidence was 4 (10%) in group M, which is lower than 37 (77.5%) in group N p-value 0.001. Group M 39 (97.5%) had better satisfaction versus 23 (53.55%) in group N, p-value 0.001 (Table IV).

Table I: Demographic and Clinical Characteristics

Variables (Mean ± SD)	M-Group n = 40 (Mean ± SD)	N- Group n = 40 (Mean ± SD)	*P*- value
Age in years	44.08 ± 9.39	44.55 ± 6.66	0.80
Weight (kg)	79.41 ± 23.81	74.86 ± 8.60	0.30
Height (m)	1.63 ± 0.07	1.619 ± 0.08	0.51
BMI (kg/m^2)	29.608 ± 7.42	28.69 ± 3.81	0.49
ASA	n (%)	n (%)	
I	15 (37.5)	18 (45.0)	
II	24 (60.0)	21 (52.5)	0.79
III	1 (2.5)	1 (2.5)	
Duration of surgery (minutes)	179.25 ± 71.10	185.68 ± 95.96	0.74
Serum magnesium (mmol/L)	0.84 ± 0.07	0.85 ± 0.21	0.65

P-value < 0.05 is significant
* Significant at 95% CI

Table II: Comparison of the mean time to first request for analgesia (min) and postoperative rescue opioid consumed in the two groups

	M-Group N = 40 (Mean ± SD)	N- Group N = 40 (Mean ± SD)	P- value
Time to first request for analgesia (min)	219.25 ± 148.88	82.25 ± 46.51	0.001*
Analgesic consumed			
Mean Rescue Pentazocine (mg)	25.45 ± 10.75	55.50 ± 15.25	0.001*
Mean No of patient who took Rescue Pentazocine (doses)	8 (20.00%)	18 (45.00%)	0.001*

P-value < 0.05 is significant
* Significant at 95% CI

Table III: Comparison of the postoperative Visual Analogue Scale pain score over 24 hours in the two groups

Hour	M- Group (Mean ± SD)	N-Group (Mean ± SD)	P- value
0	0.27 ± 0.72	2.11 ± 3.10	0.001*
1	2.82 ± 2.13	4.98 ± 1.96	0.001*
2	2.89 ± 1.57	4.40 ± 1.16	0.001*
4	4.46 ± 1.87	4.46 ± 1.71	0.965
8	3.74 ± 1.34	5.05 ± 1.39	0.001*
12	3.08 ± 0.93	4.47 ± 1.39	0.001*
24	2.26 ± 0.76	2.64 ± 1.17	0.092

P-value < 0.05 is significant
* Significant at 95% CI

Table IV: Comparison of the side effects and satisfaction score in the two groups

Side effect	M-Group n = 40 (%)	N- Group n = 40 (%)	*P*- value
PONV	4 (10.0)	31 (77.5)	0.001*
Respiratory Depression	1 (2.5)	0 (0.0)	0.314
Pruritus	0 (0.0)	2 (5.0)	0.152
Satisfaction score			
Very Unsatisfied	0 (0.0)	0 (0.0)	
Unsatisfied	0 (0.0)	2 (5.0)	0.001*
Neutral	1 (2.5)	15 (37.5)	
Satisfied	18 (45.0)	18 (45.0)	
Very Satisfied	21 (52.5)	5 (12.5)	

P-value < 0.05 is significant
* Significant at 95% CI

DISCUSSION

This study showed that 50mg/kg IV magnesium preloading improves postoperative analgesia profile in women undergoing myomectomy or TAH. Specifically, magnesium prolonged the time to the first request for rescue analgesics, lower rescue pentazocine used, VAS pain scores, and improve satisfaction scores compared to placebo, in the first 24-hours, after surgery.

These findings align with and build upon a growing body of literature supporting the role of magnesium as an effective adjunct in multimodal analgesia protocol. Our study extends these findings by evaluating both myomectomies and hysterectomies, thus broadening the gynaecologic data. Magnesium has been proven useful in African population, where analgesic adjuvants options are limited.

Magnesium's role as a physiologic blocker of NMDA receptors has been demonstrated. NMDA receptors are involved in central sensitization, and pain hypersensitivity. The receptors are located on central and peripheral neurons. NMDA receptor blockade reduces spinal cord excitability, and wind-up phenomenon, i.e., progressive increase in pain sensation with repeated stimulation. Magnesium also inhibits calcium ion channel cellular inflow at nerve terminals, which inhibits the release of excitatory pain neurotransmitters e.g., glutamate and substance P.[7,14] In addition, magnesium blocks acetylcholine and histamine release, which are important for pain stimuli transmission.[15] In this study, the time to the first request for rescue analgesics is taken as the effective postoperative analgesia period.

Similarly, Shamin et al[8] showed that following laparoscopic cholecystectomies, magnesium 50mg/kg preloading prolonged the time to the first request for rescue analgesics, 131.7 ±140.1mins compared to 49.3 ± 93.4mins in placebo. Yazdi et al[9] stated that in abdominal surgeries, 25 mg/kg magnesium, and 100 mg/kg/24-hour infusion lower postoperative NRS pain scores, and decrease rescue morphine intake, 8±3.5mg versus 13.2±5.7mg in placebo. Jarahzadeh et al[10] observed that 50mg/kg magnesium preloading lower mean VAS pain scores at 0, 1, 2, 6, and 12hour, decrease rescue narcotic used, and opioid's side effects, after hysterectomies. Tamdogan et al[11] stated that 20 mg/kg magnesium preloading, followed by 20 mg/kg/hour infusion lower rescue opioid use (35.6 ± 15.2mg compared to 44.9 ± 14.1mg in placebo), and decrease pain scores, and opioid's side effects.

Magnesium preloading has produced similar outcomes outside gynaecological procedures. Jin et al[12] in a meta-analysis of ten randomised trials of 641 patients, reported that magnesium decreases postoperative pain scores, and rescue opioid use. Singhal et al[16] stated that 50mg/kg magnesium preloading and 15mg/kg/hour infusion, reduce postoperative VAS score over 12-hours, extended rescue analgesic use period 246 mins, versus 144 mins in placebo, lower rescue analgesic pethidine consumed 181.67mg versus 251.67mg in placebo, in elective lower limb surgeries.

However, contrary to the above findings, Wilder-Smith et al[17] observed no postoperative analgesic effect with magnesium preloading. They administered magnesium 8mmol bolus and hourly for another 5 hours to women undergoing hysterectomies. Thus, the total magnesium given (48mmol) could be sub-optimal. Also, the use of 24 patients total population may have resulted to an under-powered study.

We also report that magnesium preloading lowers PONV incidence to 10% compared to 77.5% in placebo, following gynaecological procedures. This is a useful outcome since known PONV predisposing factors such as female, non-smokers, age < 50years, volatile anaesthetics, surgery beyond 90mins, perioperative opioids, and gynaecological surgeries are present in our patient population. PONV is distressing, increases the risk of gastric aspiration, and fluid imbalance.[18]

PONV results from a complex interaction of dopaminergic (D2), muscarinic (M1 and M2), serotonergic (5-HT3), histaminergic (H1), and neurokinin (NK1) neurotransmitters, the area postrema in the floor of the 4th ventricle, and the lower pons, i.e., the chemoreceptor trigger zone (CTZ), vestibular system, vagus nerve, gut, limbic system, nucleus tractus solitarius, rostral nucleus, the nucleus ambiguus, and the dorsal motor nucleus of the vagus.[18]

Similarly, Maghsoudi et al[19] stated that in 70 patients who had abdominal surgeries, magnesium 50mg/kg preloading lower PONV incidence compared to placebo. Since pain and opioid use are PONV risk factors, magnesium's opioid sparing effect may reduce PONV incidence.[20]

All patients in the magnesium group except one, were satisfied with their surgical outcome, compared to about 50% in the placebo group.

Magnesium sulphate side effects such as sedation, loss of reflexes, and oliguria, and respiratory depression were not noticed. However, the management modalities for magnesium toxicity include surveillance, use of 10% calcium gluconate 10mls over 10-15mins, and if needed, haemodialysis, cardiac and respiratory support.[21,22]

There are limitations to this study. The sample size, though adequately powered for the primary outcome, limits generalisability across diverse populations and surgical settings. Serum magnesium were not serially monitored, leaving a gap in understanding the pharmacokinetic-pharmacodynamic context. Future multicenter trials with larger cohorts and biomarker correlation may refine optimal dosing strategies.

RECOMMENDATION

Clinicians can consider magnesium 50mg/kg preloading in patient undergoing open gynaecological surgeries, for safe and effective postoperative analgesia.

CONCLUSION

This study demonstrated that 50mg/kg magnesium preloading provided effective postoperative analgesia, lower opioids use, and PONV incidence after gynaecological surgeries.

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