

Original article

# Effect of Two Doses of Magnesium Sulphate on Post-Operative Analgesia Following Emergency Exploratory Laparotomy Under General Anesthesia

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**ABSTRACT**

Opioids are frequently employed in postoperative analgesia, but their use is associated with numerous side effects, which have led to the search for non-opioid adjuncts. This study compared the effect of two doses of magnesium sulphate on post-operative analgesia following emergency exploratory laparotomy. This was a double blind randomized comparative study of ninety adult surgical patients scheduled for emergency exploratory laparotomy. Patients were randomly assigned to three groups to receive normal saline (group N), IV Magnesium sulphate 40 mg/kg over 15 mins (group MB), or IV Magnesium sulphate 40 mg/kg over 15 mins followed by an infusion of 10 mg /kg/hr till the end of surgery (group MI). The postoperative numeric rating scale for pain, time to first request for analgesia, morphine consumption, and patients' satisfaction with analgesia were measured. Age, weight, and pain scores were presented as means and standard deviations and analyzed using the Student t-test for comparisons between 2 groups and ANOVA for comparisons within 3 groups. The level of statistical significance was set at  $p < 0.05$ . There was a significant reduction (26%) in 24-hour morphine consumption ( $p < 0.001$ ) and prolongation of time to first analgesic request ( $p < 0.001$ ) in the magnesium-treated groups compared with the control. However, there was no significant difference in the numeric rating scale for pain ( $p > 0.99$ ) and patients' satisfaction with post-operative analgesia ( $p = 0.258$ ) in the three groups. This study demonstrated that the administration of magnesium sulphate reduced 24-hour morphine consumption and prolonged the time to first request for analgesia.

**Introduction**

Despite recent advances in perioperative care, a high number of patients within the African continent still experience significant postoperative pain [1-3]. Poorly treated postoperative pain can lead to respiratory problems like reduced alveolar ventilation and pneumonia; cardiovascular problems like tachycardia, hypertension, myocardial ischemia, and infarction; conversion to chronic pain, delay in wound healing, and prolonged hospital stay [4]. The medications used for the treatment of pain also cause side effects such as nausea, dizziness, and drowsiness, which are a source of discomfort to patients [5].

Surgical patients report postoperative pain as a cause of perioperative anxiety ahead of the surgical procedure itself. It is therefore a major concern to patients [6]. Postoperative pain is often managed with multimodal analgesia that employs the use of more than one analgesic technique with different mechanisms of action [7]. These techniques include intravenous paracetamol and NSAIDs, opioids and epidural analgesia. Opioids are frequently used to manage pain in a multimodal analgesia setting, but side effects such as nausea, vomiting, respiratory depression and constipation have limited their use. Other analgesic methods like epidural analgesia have limitations such as hypotension, urinary retention and lack of expertise. These challenges have led to the search for other non-opioid analgesics with fewer side effects.

The first documented clinical trial on the association between magnesium sulphate and postoperative analgesic requirement was done by Tramer and colleagues [8] in 1996. Its antinociceptive effect is related to the prevention of central sensitization caused by peripheral tissue injury [9]. The administration of intravenous magnesium sulphate has been found to result in a 30% reduction in postoperative analgesic

requirement [8,10]. However, another study challenged the previous result when it could not establish a beneficial analgesic effect for magnesium sulphate [11].

The benefits of intravenous administration of magnesium sulphate may be more evident in emergency surgical patients who have been found to have a high incidence of hypomagnesaemia [12]. Therefore, this study was carried out to determine the effect of magnesium sulphate as an analgesic adjuvant in emergency surgical patients undergoing exploratory laparotomy.

## METHODS

### **Study Setting and Design**

This study was carried out at the University of Ilorin Teaching Hospital (UIH). The hospital is a six-hundred (600) bedded tertiary hospital which serves as a referral centre for patients from the South-west and from the North-central regions of Nigeria. This was a prospective randomized double blind comparative study involving adult surgical patients scheduled for emergency exploratory laparotomy under general anaesthesia carried out from 1st of June to 30th of September 2023.

### **Ethical considerations**

Ethical approval was obtained from the University of Ilorin Teaching Hospital ethical review board before the commencement of this study (approval number ERC PAN/2023/12/0450). Oral and written informed consent, signed and dated, was obtained from all patients following a comprehensive explanation of the procedure to them by the investigator.

### **Study Population**

The subjects recruited were adult surgical patients of American Society of Anesthesiologists (ASA) physical status I to III, aged between 18 and 65years, presenting for emergency exploratory laparotomy under general anaesthesia.

### **Sample Size Calculation**

Sample size was calculated using the formula of St. George's University of London for comparing means.

$$n = [A + B]^2 \times 2 \times SD^2 / DIFF^2 [13]$$

Seyan et al [10] found a reduction in morphine consumption of 33% and a standard deviation of 0.23. The calculated sample size was 15. Assuming an attrition rate of 10% gives a sample size of 16.5, approximately 17 per group. However, in this study, 30 patients were recruited per group, making a total of 90 patients.

### **Sampling technique**

Patients were assigned to three groups (magnesium bolus group MB, magnesium bolus and infusion group MI and control group N) using a simple random sampling technique. Randomization was done by a trained research assistant. Both the patient and the researcher were blinded to the group allocation.

### **Inclusion and exclusion criteria**

All consenting patients between the ages of 18 and 65 years with American Society of Anesthesiologists (ASA) classification I to III scheduled for emergency exploratory laparotomy under general anaesthesia. Patient's refusal to participate in the study, pregnancy, hepatic or renal disease, prior treatment with calcium channel blockers, opioid analgesic abuse and known allergy to magnesium sulphate were exclusion criteria.

### **Anaesthesia management**

After routine pre-anaesthesia assessment, the patients were educated on the use of the numerical rating pain scale and the patient-controlled analgesia (PCA) infusion device. A self-designed proforma (appendix 1) was used to collect socio-demographic and medical data of the patients. All patients were weighed either in the ward or the emergency room.

After routine anaesthesia machine check, baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate (PR), peripheral arterial oxygen saturation (SpO<sub>2</sub>), temperature, and electrocardiogram (ECG) were obtained and documented.

Two intravenous lines were secured, one for fluid and the other for administration of study medications. The first three (3) milliliter blood sample for preoperative serum magnesium and albumin was collected into a plain bottle.

The study solutions were prepared by a trained research assistant, a resident doctor in the department of Anaesthesia, who did not take any further part in the study. They were administered by the researcher, who was blinded to the study groups. Patients in the N group were given 100ml of normal saline through a syringe pump in two 50 mL syringes to run over 15 min before the induction of anaesthesia. This was followed immediately by 50 ml/hr of Normal saline till the end of surgery.

Those in the MB group were given 40 mg/kg of magnesium sulphate made up to 100 ml of saline through the syringe pump in two 50 ml syringes over 15 min before the induction of anaesthesia. This was followed immediately by 50 ml/hr of normal saline administered through a syringe pump till the end of surgery.

Patients in the MI group were given 40 mg/kg of magnesium sulphate made up to 100 ml of saline through the syringe pump in two 50 ml syringes over 15 min before the induction of anaesthesia. This was followed immediately by 10 mg/kg/hr of magnesium sulphate diluted to 50 ml of Normal saline, administered through a syringe pump till the end of surgery.

The anaesthetic technique employed in all patients was general anaesthesia with endotracheal intubation.

### **Pain assessment and analgesia**

Intraoperative analgesia was maintained with intermittent boluses of fentanyl at 1.5mcg/ kg/hr and this was supplemented with intravenous paracetamol 15 mg/kg. Postoperative pain was assessed by the researcher at rest and every 15 minutes for the first hour, then hourly till 4 hours postoperative time, then 4-hourly till 24 hours postoperatively, using an 11-point Numeric Rating Scale (NRS) (0=no pain, 10=worst possible pain).

In the post-anaesthetic care unit (PACU), the time to first request for analgesia was recorded. Intravenous morphine was titrated at 2 mg every 15 minutes until the numerical pain score was  $\leq 3$  (mild pain). Total morphine consumption in the PACU was recorded.

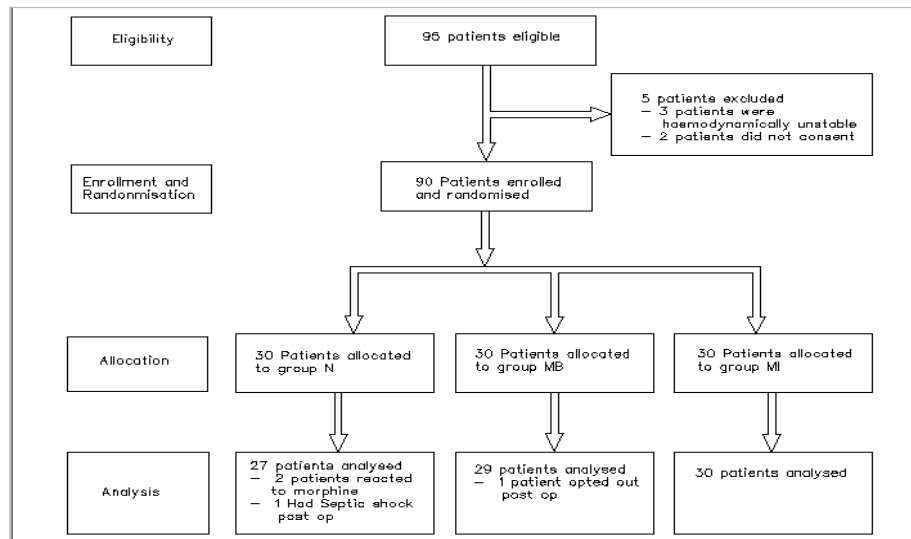
On the ward, all patients were given intravenous Paracetamol 1g 6 hourly, then Morphine was given via a patient-controlled analgesia device (Abbott Pain Management Provider Abbott Laboratories, North Chicago, USA) connected to the intravenous line, which delivered 1mg morphine bolus with 15 min lockout interval and no background infusion. Morphine consumption was recorded at the 1<sup>st</sup>, 2<sup>nd</sup>, 4<sup>th</sup>, 12<sup>th</sup>, and 24<sup>th</sup> hours after the operation by the researcher. Patient's satisfaction with pain relief was assessed 24 hours after the operation using a 5-point satisfaction score on a Likert scale.

### **Statistical analysis**

The data obtained was analyzed using the Statistical Package for Social Sciences (SPSS) software version 20. Categorical data such as gender, NRS for pain score and ASA classification was represented as frequency, proportion, median and range. Analysis was done using the chi-square test. Continuous variables such as age, weight, time to first request for analgesia and total morphine consumption were presented as mean, standard deviations, and associations in the three groups were compared using the Analysis of Variance (ANOVA) test while associations between groups were determined by the Turkey post hoc analysis. Patient satisfaction with the post-operative analgesia was represented as frequency, percentiles, and was analysed using the Mann-Whitney U test. Statistical significance was assumed for  $P < 0.05$ .

### **RESULTS**

A total of 90 patients (30 in each group) were recruited from June 2<sup>nd</sup> 2023, to 2<sup>nd</sup> October 2023. Eighty-six (86) patients out of the 90 patients that were randomized completed the study. Two patients from the control (N) group had an allergic reaction to morphine in the recovery room and were withdrawn from the study. One patient from the MI group opted out of the study on the ward because his IV line got tissue and did not want the IV access to be reset. The last patient from the N group could not complete the study because he went into septic shock.



**Figure 1: Consort Flow Diagram**

### Demographic Characteristics

The mean ages were  $46.00 \pm 12.58$  yrs,  $41.70 \pm 12.70$  yrs and  $40.78 \pm 14.91$  years in groups MB, MI, and N, respectively ( $p = 0.30$ ), while the mean weights in the three groups were  $56.93 \pm 11.87$  kg,  $59.5 \pm 10.29$  kg and  $62.11 \pm 15.33$  kg in the MB, MI and N groups, respectively ( $p = 0.31$ ). In group MB, the mean height was  $1.68 \pm 0.06$  m, while it was  $1.67 \pm 0.08$  m in group MI and  $1.64 \pm 0.09$  m in group N ( $p = 0.16$ ). There was no significant difference in the gender, ASA status, weight, height and BMI across the three groups ( $p = 0.18$ ,  $0.70$ ,  $0.31$ ,  $0.16$  and  $0.18$  respectively) (Table 1).

**Table I: Comparison of the patient's demographic data and ASA grading**

Variable	Group MB (n =29)	Group MI (n =30)	Group N (n =27)	P value
Age (years)	$46.00 \pm 12.58$	$41.70 \pm 12.70$	$40.78 \pm 14.91$	0.296
Weight (kg)	$56.93 \pm 11.87$	$59.5 \pm 10.29$	$62.11 \pm 15.33$	0.310
Height (m)	$1.68 \pm 0.06$	$1.67 \pm 0.08$	$1.64 \pm 0.09$	0.158
BMI(Kg/m <sup>2</sup> )	$20.34 \pm 4.20$	$21.28 \pm 4.14$	$22.67 \pm 4.43$	0.155
Gender (M /F)	22/7*	24/6*	16/11*	0.184
ASA I/II/III	2/10/17*	1/16/13*	4/9/14*	0.704

Mean  $\pm$ SD (ANOVA). \*Frequency and proportion (Chi-square)

### Twenty-four-hour morphine consumption

Morphine consumption in 24 hours was lowest in the magnesium bolus plus infusion group (MI) with a mean of  $31.40 \pm 8.37$  mg. Both the MB group and the MI group had significantly lower morphine consumption than the control group ( $p < 0.0001$ ). There was no significant statistical difference in morphine consumption between the two-magnesium sulphate treated groups ( $p = 0.71$ ) (see Table II).

### The time to first request for analgesia

The time to first request for analgesia was longest in the MB group with a mean value of  $45.97 \pm 20.30$  mins, and was shortest with N group with a mean value of  $27.03 \pm 10.92$  mins. The mean value for MI group was  $35.23 \pm 12.34$  mins ( $p < 0.0001$ ). There was no significant difference in the meantime to first request for analgesia in the MI vs N group,  $p = 0.096$ . However, a significant increase in time to first request for analgesia existed in MB vs MI group,  $p = 0.020$ , and MB vs N,  $p < 0.0001$  (Table II).

There was a significant increase in the duration of surgery across the 3 groups ( $p = 0.008$ ). The duration of surgery was longest in the MB group with a mean value of  $176.07 \pm 80.15$  mins, then  $147.30 \pm 54.88$  mins in the MI and, and  $122.50 \pm 57.89$  mins in the normal saline group. There was a statistically significant increase in the duration of surgery between MB vs N group with  $p = 0.006$  (Table II).

**Table II: Total morphine consumption in 24hrs, Time to first request for analgesia, and duration of surgery.**

Variable	Group MB	Group MI	Group N	P value MB vs MI vs N	P value MB vs MI	P value MB vs N	P value MI Vs N
Total morphine consumption	33.07±6.23	31.40±8.37	44.48±9.55	<0.0001	0.711	<0.0001	<0.0001
Time to 1 <sup>st</sup> request for analgesia (mins)	45.97±20.30	35.23±12.43	27.03±10.92	<0.0001	0.020	<0.0001	0.096
Duration of surgery (mins)	176.07±80.15	147.30±54.88	122.50±57.89	0.008	0.208	0.006	0.309

**Post-operative pain scores**

There was no significant difference in the NRS for pain scores post operatively in almost all the time periods (p=0.75) except at 1hr. The median NRS for pain scores were lowest within the first 15 - 30 postoperative minutes, highest at 30 - 60 mins in the control group and 45 - 60 mins in the magnesium treated groups. The patients were pain free for the rest of the study period (Table III).

**Table III: Comparison of post-operative pain score**

Immediate post op	Group MB(n=29)	Group MI(n=30)	Group N(n=27)	P value
	0 (0-0)	0(0-0)	0(0-0)	>0.999
15mins	0(0-0)	0(0-0)	0(0-0)	0.695
30 mins	0(0-0)	0(0-5)	7(5-8)	0.628
45 mins	4(1-6)	5(0-5)	4(2-5)	0.747
60mins	3(2-7)	1(0-4)	2(0-2)	0.004
2hrs	0(0-0)	0.(0-0)	0(0-0)	0.537
8hrs	0(0-0)	0(0-0)	0.(0-0)	>0.999
12hrs	0(0-0)	0(0-0)	0.(0-0)	>0.999
16hrs	0(0-0)	0.(0-0)	0(0-0)	>0.999
20 hrs	0(0-0)	0(0-0)	0(0-0)	>0.999
24hrs	0.(0-0)	0(0-0)	0(0-0)	>0.999

Median (interquartile range), p-value, Chi-square

**Patient satisfaction with the level of analgesia**

The level of patient satisfaction across the groups was high with 84 (97.7%) reporting complete satisfaction. This was distributed as 28 (96.6%) in the MB group, 30 (100%) in the MI group and 26 (96.3%) in the N group. There was no significant difference in patient satisfaction with the level of analgesia in the 3 groups (p = 0.309 (Table IV).

**Table IV: Patients' satisfaction with pain relief**

Likert score	Group MB(n=29)	Group MI(n=30)	Group N(n=27)
1 (Completely dissatisfied)	0(0 %)	0(0%)	0(0%)
2 (Dissatisfied)	0(0 %)	0(0%)	0(0%)
3 (Neither satisfied nor dissatisfied)	1(3.3%)	0(0%)	1(3.3%)
4 (Satisfied)	0(0%)	0(0%)	0(0%)
5 (Completely satisfied)	28 (96.6%)	30(100%)	26 (96.3%)

No significant difference p-value>0.05, Frequency (%)

## Discussion

This study found that the administration of magnesium sulphate to patients undergoing exploratory laparotomy significantly reduced postoperative morphine consumption within the first twenty-four hours and prolonged the time to first analgesic request.

The index study demonstrated a morphine sparing effect for magnesium sulphate, as 24 hours total morphine consumption was significantly reduced in patients who were pretreated with magnesium sulphate compared with the control ( $p < 0.0001$ ). The mean morphine consumption was highest in the control group, but least in the MI group, although no significant difference existed between the MI and MB group ( $p = 0.711$ ). Total morphine consumption in 24 hours was 26% less in the magnesium-treated patients compared to the control group. The findings are comparable to those of Tramer et al [8], who found a 30% reduction in morphine consumption in the magnesium-treated group. This finding suggests that intravenous magnesium sulphate as an analgesic adjuvant has a morphine sparing effect. Also, other studies that found an opioid sparing effect used larger doses of magnesium than the index study. Tramer<sup>8</sup> administered a 3g bolus and 10g infusion of magnesium sulphate, while Yazdi [14] administered the infusion dose intraoperatively and for 24 hours postoperatively. This study showed that lower doses of magnesium sulphate, restricted to the intraoperative period, were efficacious in producing an opioid sparing effect.

Furthermore, the index study enrolled emergency procedures while the Tramer et al [8] study enrolled elective procedures, suggesting that the analgesic effects of magnesium are evident both in elective and emergency surgeries.

The antinociceptive action of magnesium is from the inhibition of calcium influx into neurons through NMDA receptor blockade in the brain which prevents central sensitization and reduces neuronal excitability [15]. NMDA receptor antagonism also prevents pain hypersensitivity phenomena responsible for persistent pain after the original injury has healed. A systematic review has found that the perioperative intravenous administration of magnesium attenuates postoperative pain intensity [16].

The NRS for pain scores in the first 15 – 30 mins were low, probably due to the residual effect of anaesthesia, which had not fully worn off. However, between 30 and 60 mins, pain scores were the highest, probably because this was the period when the effect of anaesthesia was wearing off but postoperative analgesia had not fully taken effect. It may be prudent to commence postoperative analgesia within the first 30 mins to ensure a seamless transition from intraoperative to postoperative analgesia without undue patient discomfort. The index study did not show any significant difference in the NRS for pain scores across the three groups except at 60 minutes ( $p = 0.04$ ). The low pain scores in the groups were probably because all the patients had access to adequate analgesia, resulting in no difference in the pain scores in all three groups. This finding is similar to the reports by other studies [8,11,17]. However, another systematic review found the pain scores to be less in participants who were administered magnesium [18] In the index study, at 2hr post operatively, all the patients had probably achieved a peak plasma concentration of morphine and were therefore pain-free, as demonstrated by pain scores 0 till the end of the study period. The peak time of highest pain score at 30minutes for MB group and 60 minutes for the MI group was because the patient had not been able to titrate morphine to achieve a good pain control, especially the magnesium-treated patients who were just requesting for analgesia at that time. Magnesium is a physiological inhibitor of calcium channels by blocking NMDA receptors, which causes the antinociceptive effect; however, its mechanism of pain relief remains unknown.

Time to first request for analgesia in the index study was significantly longer in the magnesium-treated groups compared to the control ( $p < 0.001$ ). This is similar to findings by another study [18]. This also buttresses the fact that magnesium sulphate has an effective analgesic effect when administered as an adjuvant. This will also help to reduce the dose of analgesics, especially opioids, and their attendant side effect. Surprisingly, the magnesium bolus group had a more prolonged time to first analgesic request than the magnesium bolus and infusion group. The longer duration of surgery experienced by participants in the magnesium bolus group may have impacted the time to first analgesic request. The prolonged time to first analgesic request may be from the repeated doses of analgesic agents administered intraoperatively and not the influence of magnesium sulphate.

The index study did not show any significant difference in patients' satisfaction with post-operative analgesia. ( $p = 0.58$ ). Patients' satisfaction with analgesia has been described as a complex psychological entity which may be influenced by numerous factors, other than analgesia, such as the educational status of the patient, waiting time to get analgesia, and the level of information the patient received on pain [19]. Consequently,

factors other than the effectiveness of pain control can influence patient satisfaction with analgesia. This may explain why studies like the index one and the one by Buli et al [19] could not find an association between good analgesia and patient satisfaction.

### Limitations of the study

The heterogeneity of the surgical procedure (exploratory laparotomy for ruptured appendix is different from gangrenous bowel or typhoid perforation) was a limitation, as the degree of surgical intervention varied from one patient to another. The duration of surgery also varied from group to group. Patient in the MB had a longer duration, whereas duration of surgery for MI and N group were similar, this may have affected subsequent post-operative data collected for example time to first request for analgesia.

### Conclusion

This study demonstrated that perioperative administration of magnesium sulphate significantly prolonged the time to first request for analgesia, and reduced 24hrs morphine consumption in adult patients undergoing emergency abdominal surgeries.

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