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sameh seyam
*Department of Anesthesia and Intensive care, Faculty of medicine for male, Al-Azhar University, Cairo 12992, Egypt.*, sameh_icu1@yahoo.com

khaled elsheshtawy
*Department of Anesthesia and Intensive care, Faculty of medicine for male, Al-Azhar University, Cairo 12992, Egypt.*, khaledshrief2@gmail.com

mohamed morsy
*Department of Anesthesia and Intensive care, Faculty of medicine for male, Al-Azhar University, Cairo 12992, Egypt.*, mohamedalianesthesia@gmail.com



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Anesthesia

# The Effect of Epidural Magnesium Sulfate as An Adjuvant to Fentanyl for Postoperative Analgesia after Lower Limb Orthopedic Surgery

**Seyam Sameh Hamdi[1,*] MD, Elsheshtawy Khaled[1] MD, Morsy mohamed[1] A. MD**

***Corresponding Author:***
Seyam Sameh Hamdi

*sameh_icu1@yahoo.com*

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*[1]Anasthesiology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.*

**ABSTRACT**

**Background**: Magnesium, a physiological antagonist of calcium and N-methyl-D-aspartate receptors (NMDA), has a role in the prevention of pain in patients undergoing different surgeries.

**Patients and Methods:** This prospective randomized double-blinded controlled study was conducted on 60 patients undergoing lower extremities arthroscopic surgery. Spinal anesthesia was given to all patients and epidural catheters inserted at L4/ L5 or L3/ L4 inter-space, prior to surgery for postoperative pain management. Postoperatively, the patients were randomly allocated into three equal groups**.** Group I (Control S group; n 20 patients) patients received epidural saline at a rate of 1ml/h for 24 hours. Group II (MI; n 20 patients) patients received epidural 50mg magnesium sulfate in 5ml volume of normal saline as a bolus dose followed by continuous epidural infusion of 100mg at a total of 24ml volume for 24 hours at a rate of 4mg/h. Group III (M II; contain 20 patients) patients received epidural 50mg magnesium sulfate in 5ml volume of normal saline as a bolus dose followed by continuous epidural infusion of 500mg at a total 24ml volume for 24 hours at a rate of 20 mg/h. All patients will be provided with a syringe pump device and the primary setting of background infusion of fentanyl 3 mic/ml at a rate of 10 ml/h via an epidural catheter. The visual analog score, vital signs, time of the first request for rescue analgesia, motor block, need for supplemental analgesic and adverse effects were recorded in the postoperative period.

**Results**

VAS scores were significantly lower in both MI and MII groups as compared with the control group at the 1st hour and the 2nd hour of the postoperative course.

**Conclusion**

The addition of epidural magnesium sulfate for postoperative epidural analgesia provided a pronounced significant reduction in postoperative rescue analgesia with no significant difference between the two magnesium doses and minimal side effects.

**Keywords:** Lower extremities; orthopedic surgeries; magnesium sulfate; epidural.

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**Authorship**: *all authors have contributed to the article.*

## INTRODUCTION

Regional anesthesia is a competent, cheap procedure, with the advantage of postoperative pain relief. Adequate treatment of post-operative pain blunts autonomic, somatic, and endocrine responses. [1]

It has become a common tradition to use a poly-pharmacological strategy for the treatment of postoperative pain because no drug has yet been classified that specifically hinders nociception without associated side effects. [2]

Epidural analgesia is usually implemented using a mixture of local anesthetic and an opioid (typically a lipophilic opioid). Compared with opioids or local anesthetic alone, a local anesthetic-opioid mixture affords superior postoperative analgesia with less local anesthetic doses. [3]

Epidural opioids award several advantages when compared with epidural local anesthetics, related principally to the vacancy of sensory and motor block as well as the lack of sympathetic block. [4]

Unluckily, an epidural and intra-spinal opioid can be affiliated with dose-dependent side effects including nausea, vomiting, urinary retention, respiratory depression, pruritis and development of tolerance and physical dependence. [5]

Other classes of drugs have been investigated more recently to try to promote the quality of neuraxial blockade, both in the subarachnoid space and in the epidural space. [6]

Magnesium is the 4th most liberal cation in the body. It has antinociceptive outcomes in human and animal patterns of pain, it has also been stated that it can exhibit the analgesic

characteristics of opioids [7], these results are essentially based on the control of calcium influx into the cell that is typical physiological calcium opposition and opposition of NMDA receptors. [8]
So this study was designed to emit more light on this topic and to study the effect of two dosed of epidural magnesium sulfate infusions on postoperative analgesia as well as to study its effect as an adjuvant to fentanyl for postoperative analgesia.

The aim of this work is to investigate the effects of two concentrations of epidural magnesium sulfate infusions on postoperative analgesia in patients undergoing lower extremities orthopedic surgery. The primary outcome will be the level of pain relief and secondary outcomes will be the level of patient satisfaction and the occurrence of adverse effects.

**Sample size calculation:**

The minimal sample size was 60 divided into three groups. To attain a power of test 90% at an alpha error of 0.05, we included 20 patients in each group. Statistical analysis was performed with IBM SPSS version 21.0 software. Mean and the standard deviation was calculated for age, weight, and postoperative analgesia requirements; independent student t-test was used. Frequency and percentages were used for descriptive parameters. A chi-square test was used to compare parameters.

## PATIENTS AND METHODS

This prospective randomized controlled double-blinded study was carried on 60 patients of both sexes, after permission from the ethics committee of Al-Azhar university hospitals and getting informed written consent. The study was carried in Al-Azhar University hospitals from April 2015 to November 2016. Inclusion criteria were: age between 21 and 60 years, American Society of Anesthesiologists (ASA) I and II physical status, and listed for orthopedic lower limb procedures. Patients with evidence of any major systemic disease or a history of allergy to any of the medicines in the study were omitted from the study.

Standard monitoring escorted, baseline hemodynamic readings were recorded. Once intravenous access had been achieved an infusion of ringer lactate started (10ml/Kg over 20- 30 minutes), Spinal anesthesia was given to all patients and epidural catheters inserted at L4/ L5 or L3/ L4 inter-space, prior to surgery for postoperative pain management. Preoperatively, all patients will be familiarized with the visual analog pain scales (VAS) that consisted of an unmarked 10cm line, with 0cm; no pain, 10cm; worst pain ever).

Spinal anesthesia was conducted at L3-4 or L4-5 interspace with 12.5 mg 0.5% heavy bupivacaine, using a 25 G Quincke needle. During the course of surgery, epidural bupivacaine 0.5% will be supplied, if required. The sensory block will be evaluated bilaterally by using pinprick with a short needle; Motor block will be assessed using a modified Bromage scale (Bromage, 1965).[9] No analgesic or sedative drugs were used intraoperatively to avoid interruption with the outcomes of the study.

At the end of the procedure, patients will be randomized by a sealed envelope method, into one of three groups. All patients will be provided with an epidural syringe pump device and both magnesium sulfate and fentanyl infusions started. The primary setting of background infusion of fentanyl 3 mic/ml at a rate of 10 ml/h.

Group I (Control group (S) group; n=20 patients) Patients will receive epidural normal saline at a rate of 1ml/h for 24 hours plus epidural fentanyl via another infusion pump. Group II (MI); n=20 patients) Patients will receive epidural 50 mg magnesium sulfate (phenol-free) (Otsuka pharm, Egypt) in 5ml volume of normal saline as a bolus dose followed by continuous epidural infusion of 100 mg at a total 24ml volume for 24 hours at a rate of 4mg/h. Group III (MII); contain 20 patients) Patients will receive epidural 50mg magnesium sulfate in 5ml volume of normal saline as a bolus dose followed by continuous epidural infusion of 500 mg at a total 24ml volume for 24 hours at a rate of 20 mg/h.

All patients were observed at time intervals 30 minutes, 1, 2, 3, 4, 6, 12, 18 and 24 hourly in the postoperative period for 24 h for the following parameters: mean arterial blood pressure (MABP), heart rate (HR), Sp02, respiratory rate, time of first request for rescue analgesia (usually associated with VAS >3), motor block using a modified Bromage scale,[9] and need for supplemental analgesia. Supplemental analgesia was administered with (pethidine) 50 mg intramuscular injection if VAS greater than 3 and the total consumption of pethidine was recorded over 24 h. Adverse events like nausea, vomiting, pruritus, and respiratory depression were recorded. The study medications were arranged by one anesthetist and injected by another anesthetist who was blinded to the study medicines. The nurse who was inspecting the patient and recording the postoperative study parameters was also blinded to the study medicines.

Statistical presentation and analysis of the present study were conducted, using the mean, standard error, student t-test, paired t-test, Chi-square, Linear Correlation Coefficient and ROC curve by SPSS v 17.

## RESULTS

As regards demographic data, ASA, and type of surgery, there were no significant differences among all groups as shown in Table (1) and (2) (P>0.05).

| | | Group | | | | | | Total | | Chi-square | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | | M I | | M II | | | | | |
| | | N | % | N | % | N | % | N | % | $X^2$ | P-value |
| Gender | Female | 14 | 70.0% | 12 | 60.0% | 14 | 70.0% | 40 | 66.7% | 0.592 | 0.744 |
| | Male | 6 | 30.0% | 8 | 40.0% | 6 | 30.0% | 20 | 33.3% | | |
| ASA | ASA I | 12 | 60.0% | 10 | 50.0% | 12 | 60.0% | 34 | 56.7% | 1.183 | 0.881 |
| | ASA II | 6 | 30.0% | 6 | 30.0% | 6 | 30.0% | 18 | 30.0% | | |
| | ASA III | 2 | 10.0% | 4 | 20.0% | 2 | 10.0% | 8 | 13.3% | | |
| Type of operation | Intramedullary nailing | 6 | 30.0% | 8 | 40.0% | 5 | 25.0% | 19 | 31.7% | 3.735 | 0.712 |
| | Dynamic hip screw | 9 | 45.0% | 9 | 45.0% | 7 | 35.0% | 25 | 41.7% | | |
| | Cannulated screw | 2 | 10.0% | 1 | 5.0% | 4 | 20.0% | 7 | 11.7% | | |
| | Total hip replacement | 3 | 15.0% | 2 | 10.0% | 4 | 20.0% | 9 | 15.0% | | |

**Table 1:** Patient characteristics and type of surgery

| | | Group | | | | | | ANOVA | |
|---|---|---|---|---|---|---|---|---|---|
| | | Control | | FM I | | M II | | F | P-value |
| Age(years) | Mean±SD | 41.63 | ± 10.60 | 43.32 | ± 8.46 | 41.74 | ± 7.59 | 0.221 | 0.802 |
| Ht(meter) | Mean±SD | 1.66 | ± 0.03 | 1.67 | ± 0.05 | 1.67 | ± 0.04 | 0.331 | 0.720 |
| Wt(kg) | Mean±SD | 76.95 | ± 6.04 | 74.77 | ± 6.43 | 75.56 | ± 7.30 | 1.555 | 0.235 |
| BMI | Mean±SD | 27.90 | ± 2.38 | 26.70 | ± 2.97 | 27.16 | ± 3.04 | 1.385 | 0.341 |

**Table 2:** Patient characteristics of the studied groups

When analyzing the VAS of the three groups, the patients in the control group showed the highest VAS all through the postoperative phase. It was found that there is a significant statistical difference at the 1st hour and the 2nd hour of the postoperative course when comparing the control group with the M I group and M II group. But there was no significant statistical difference when comparing the three groups at the other time points of the postoperative course as shown in Figure1 and Table 3.

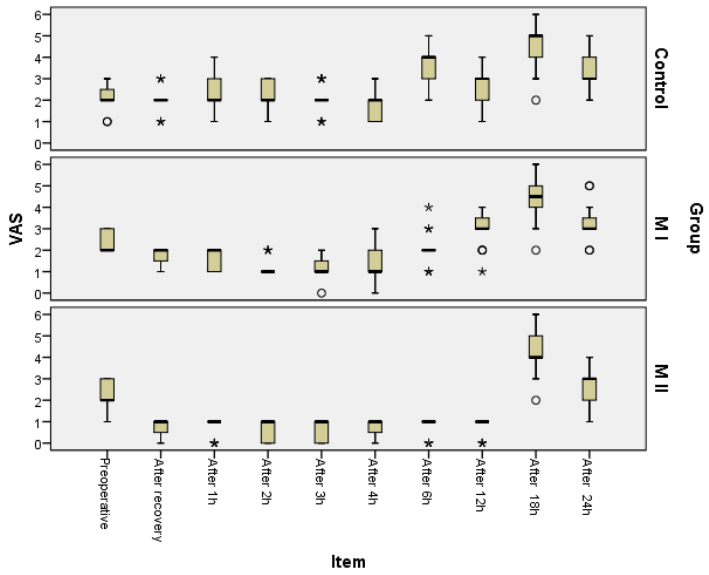


**Fig.1:** VAS of the study groups

| | | Group | | | Kruskal-Wallis Test | |
|---|---|---|---|---|---|---|
| | | **Control** | **M I** | **M II** | **$X^2$** | **P-value** |
| **VAS1** | **Range** | 0-3. | 0-3. | 0-3. | 0.612 | 0.736 |
| | **Median(IQR)** | 0(1) | 0(1.75) | 0(1) | | |
| **VAS2** | **Range** | 2-5. | 1-4. | 1-3. | 13.695 | 0.001* |
| | **Median(IQR)** | 2.5(1) | 1(2) | 1(1) | | |
| **VAS3** | **Range** | 4-Feb | 2-4. | 3-4. | 12.726 | 0.002* |
| | **Median(IQR)** | 2(1.75) | 2.5(2) | 4(1) | | |
| **VAS4** | **Range** | 3-4. | 3-4. | 3-4. | 0.539 | 0.764 |
| | **Median(IQR)** | 4(1) | 4(1) | 4(1) | | |
| **VAS5** | **Range** | 3-4. | 2-4. | 2-4. | 14.620 | 0.001* |
| | **Median(IQR)** | 4(1) | 3(1.75) | 2(1) | | |
| **VAS6** | **Range** | 2-3. | 1-3. | 1-3. | 0.561 | 0.755 |
| | **Median(IQR)** | 2(1) | 2(1) | 2(2) | | |
| **VAS7** | **Range** | 1-2. | 1-3. | 1-2. | 7.990 | 0.018* |
| | **Median(IQR)** | 1(0.75) | 1.5(0.75) | 1(1) | | |
| **Friedman Test** | **$X^2$** | 89.812 | 71.656 | 87.725 | | |
| | **P-value** | <0.001* | <0.001* | <0.001* | | |
| **Mean rank** | **VAS1** | 1.50 | 2.10 | 1.68 | | |
| | **VAS2** | 4.55 | 3.45 | 2.95 | | |
| | **VAS3** | 4.23 | 5.13 | 6.33 | | |
| | **VAS4** | 6.13 | 6.13 | 6.15 | | |
| | **VAS5** | 5.90 | 5.38 | 4.55 | | |
| | **VAS6** | 3.78 | 3.83 | 3.70 | | |
| | **VAS7** | 1.93 | 2.00 | 2.65 | | |

**Table 3:** VAS readings of the three groups

As regards time for first analgesic demand, there was no statistically significant difference between the control group (40.380 ± 10.258 min) and M I group (41.912 ± 10.166 min) and M II (40.358 ± 9.445 min) with P-value 0.852 as shown in Table 4.

| | | Group | | | ANOVA | |
|---|---|---|---|---|---|---|
| | | Control | M I | M II | F | P-value |
| | Mean±SD | 40.38 ± 10.25* | 41.91 ± 10.16* | 40.35 ± 9.44* | 0.161 | 0.852 |

*Time is expressed in hours.
**Table 4:** Time for the first analgesic request (hours)

As regards the total consumptn of fentanyl per 24 hours, epidural fentanyl infusion was fixed for all groups with another epidural syringe pump device and the primary setting of background infusion of fentanyl 3 mic/ml at a rate of 10 ml/h. Regarding total analgesic (pethidine) requirement it was significantly lower in both M I and M II groups than in the control group with p-value < 0.001 as in the control group, the total consumption was (144.215±18.18) mg while there was no significant difference between the two magnesium groups as in the M I group, the total consumption was (103.25±13.20) mg, while in the M II group, the total consumption was (97.24±10.28) mg, with p-value (0.480) (Table 5)

| | Group | | | ANOVA | |
|---|---|---|---|---|---|
| | Control | M I | M II | F | P-value |
| Mean±SD | 144.21 ±18.18* | 103.25 ±13.20* | 97.24 ±10.28* | 35.247 | 0.00 |
| Tukey's test | Control& M I | Control& M II | M I& M II | | |
| | <0.001** | <0.001** | 0.480 | | |

** Statistically significant difference (p<0.001)
*Dose expressed in mg.
**Table 5:** Total analgesic requirements

As regards motor block assessment using a modified Bromage scale, there was no difference between all groups either intraoperatively or postoperatively.

As regards the HR, MAP, SpO2, and respiratory rate showed no statistically significant difference among all groups in the postoperative periods (P>0.05) as shown in table 6.

| | | Group | | | ANOVA | |
|---|---|---|---|---|---|---|
| | | Control | M I | M II | F | P-value |
| MAP1(30min.) | Mean±SD | 124.35 ± 8.774 | 124.95 ± 8.042 | 125.50 ± 6.53 | 0.108 | 0.898 |
| MAP2(1h) | Mean±SD | 124.30 ± 7.15 | 124.70 ± 7.64 | 121.05 ± 8.00 | 1.385 | 0.259 |
| MAP3(2h) | Mean±SD | 124.55 ± 7.74 | 125.95 ± 6.24 | 123.70 ± 6.45 | 0.550 | 0.580 |
| MAP4(6h) | Mean±SD | 124.10 ± 5.02 | 125.25 ± 6.90 | 123.95 ± 7.92 | 0.224 | 0.800 |
| MAP5(12h) | Mean±SD | 123.75 ± 7.46 | 125.40 ± 7.30 | 125.85 ± 6.83 | 0.470 | 0.627 |
| MAP6(18h) | Mean±SD | 124.65 ± 7.11 | 123.70 ± 7.29 | 124.75 ± 7.13 | 0.130 | 0.878 |
| MAP7(24h) | Mean±SD | 126.65 ± 8.16 | 123.00 ± 6.71 | 125.25 ± 8.57 | 1.098 | 0.340 |

**Table 6:** Patient MAP in relation to surgery* readings are expressed in mmHg.

This study did not record any significant epidural drug-related or any significant neurological adverse effects postoperatively.

## DISCUSSION

The present study revealed that adding 500 mg magnesium sulfate to epidural fentanyl post-operatively as compared with 100 mg concentration is associated with a shortening of the time to reach the sensory and motor blockade, prolongation of both postoperative analgesia, and time for the first analgesic dose without hemodynamic influence or complications.

Regarding the route of administration whether intravenous, epidural, or intrathecal, the exact site of action of magnesium is presumably at the spinal cord NMDA receptors. Magnesium is an NMDA receptor antagonist that inhibits the central sensitization from peripheral painful stimulus regulated by NMDA receptors. [10]

This consequence is principally based on physiological calcium antagonism, by voltage-dependent control of calcium entry into the cell. [11]

In earlier trials, Magnesium sulfate was confirmed to be an efficient adjuvant when combined with bupivacaine in epidural anesthesia during various surgeries such as orthopedic surgeries and cesarean section, [12] [13] [14]or when combined with levobupivacaine in subarachnoid anesthesia during major orthopedic procedures.[15]

Few studies examined the effect of adding magnesium sulfate to epidural fentanyl on postoperative analgesia. Furthermore, most of the trials that assessed the postoperative analgesic outcome of epidural magnesium sulfate used a single dose of epidural magnesium, either added postoperatively or preoperatively.

Kandil *et al.* [14] investigated the prophylactic use of epidural magnesium sulfate to decrease narcotic demands in orthopedic procedures.

They noticed that combining magnesium with epidural bupivacaine is correlated with a significant change in VAS and a significant decrease in the number of patients demanding early postoperative analgesia as well as total fentanyl consumption.

Hassanein *et al.* [15] investigated the effect of a single dose of 50 mg magnesium sulfate via epidural rout as an adjuvant to bupivacaine 0.125% and 50 µg fentanyl for painless labor. It was associated with a longer duration of action, quicker onset, and decreased the progressing pain with no adverse effects on parturient and fetus assessed by Apgar score, fetal heart rate, and cord blood acid-base state.
Banwait et al. [16] used combined epidural-spinal anesthesia for sixty patients undergoing hip replacement procedures, they investigated the postoperative analgesic effect of single-dose 75 mg magnesium sulfate combined with epidural fentanyl 1 µg/kg at the end of the procedure in comparison to epidural fentanyl 1 µg/kg alone. They found that it was associated with more continued analgesia and fewer analgesic requirements than that observed with epidural fentanyl only.

The results we found in the present study are in agreement with the results in these results in that epidural magnesium sulfate lengthens postoperative analgesia without adverse effects, the main contrasts between them and the present study are using only single dose of epidural magnesium sulfate either preoperative or postoperative and the nature of procedures which are restricted to hip replacement surgery but we introduced other lower limb surgeries in the present

study which include total knee replacement, total hip replacement, and other surgeries in most utmost of the patients.

In accordance with the present study, Farouk et al. [17] assessed the analgesic effect of magnesium when combined with a multimodal patient-controlled epidural analgesia (PCEA) on 90 patients listed for total abdominal hysterectomy under general anesthesia, patients allotted into three groups. Group (1) received a dose of epidural magnesium 50 mg before the induction of general anesthesia, followed by an infusion of 10 mg/h till the end of surgery. Group (2) received epidural normal saline during the same duration and a single dose of epidural magnesium 50 mg at the end of surgery. Group (3) received epidural normal saline infusion during all three times (control group) In that study, Farouk et al. [17] Shortly postoperatively and maintained for three days, patients in the two magnesium groups received PCEA with magnesium 1mg/ml, fentanyl 1 µg/ml, and bupivacaine 0.08%, while patients in the control group received PCEA with bupivacaine 0.08% and fentanyl 1 µg/ml. Lower analgesic demand and lower pain scores were reported in the first group compared to the second and control groups, and in the second compared to the control group, with no reported adverse events.

A modern related study was performed by Radwan *et al*.[18] and included 66 aged patients listed for a lumbar discectomy and laminectomy procedure at a single level under general anesthesia. in the preoperative phase, patients were allotted into three groups; Group (1) received 14 ml levobupivacaine 0.5% and 1 ml normal saline, Group (2) received 14 ml levobupivacaine 0.5% + 50 mg magnesium sulfate, and Group (3) received only14 ml levobupivacaine 0.5% + 50 µg fentanyl but no magnesium sulfate. After induction of general anesthesia, epidural infusion at a rate of 5 ml/h started continuously as follows: Group (1) received levobupivacaine 0.125% only, Group (2) received levobupivacaine 0.125% + 2 mg/ml magnesium sulfate, and Group C received levobupivacaine 0.125% + 4 µg/ml fentanyl.

The second and third groups were similar regarding hemodynamic affection. Motor and sensory onset were faster significantly in the second group compared to the first and third groups. The second and third groups were similar concerning postoperative analgesia as they had a more extended continuance of analgesia than the control group with a less number of patients requiring either one or more doses of analgesia. The main contrasts between the present study and Radwan *et al*. [18] study are the character of operation with shorter skin incision and without traction on the viscera, smaller sample size, age of patients which is 65 years old and higher, type of anesthetic method which is combined epidural and general anesthesia, and further i.v. injection of fentanyl in a dose of1.5 µg/kg was started at the induction of general anesthesia in the three groups, and lastly the use of less dose of levobupivacaine, 0.125%, during intraoperative epidural infusion.

This study did not record any significant epidural drug-related or any significant neurological adverse effects postoperatively. These results agree with some of the trials that have previously examined the neurological adverse effects of using epidural Mg sulfate.

## CONCLUSION

The addition of magnesium sulfate to epidural infusion for postoperative analgesia afforded a noticeable significant decline in intensity of postoperative pain with few adverse effects. It was observed that the impact of magnesium sulfate seems to be dose-dependent. It was also noticeable that no significant difference between the two Mg sulfate doses which may make the lower dose tip weighted.

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