



The effect of epidural magnesium sulphate on postoperative nociception and serum B endorphin levels in high tibial osteotomy orthopedic surgery

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ABSTRACT

Background: Epidural magnesium sulphate provides better analgesia and opioid-sparing effect postoperatively. B-endorphins plasma levels are inversely related to the severity of pain. We investigated the possible relationship between epidural magnesium sulphate, postoperative analgesia and serum beta-endorphin levels in high knee osteotomy orthopedic surgery.

Methods: Sixty patients of both sexes, aged between 18 and 65 years, ASA I or II scheduled for high tibial osteotomy were divided to two groups (30 patients each): control group, received epidural bupivacaine 0.5%, lidocaine 2% and saline; and (Mg group) received epidural bupivacaine, lidocaine and magnesium sulphate (50 mg/10 ml saline). Venous blood samples were withdrawn to measure serum B endorphin levels (SBE), at different time intervals. We recorded time to first analgesic requirement, pain numeric rating score (NRS) and postoperative hemodynamic variables and incidence of complications.

Results: Time to first analgesic request was significantly longer in Mg group (pain score less than 5) compared to control group ($P < 0.05$) also the frequency and number of analgesic requests were significantly less in the Mg group than in the control group $P = 0.000$. B endorphins level was significantly lower in the Mg group than in the control group after 4 h of epidural insertion ($P = 0.004$).

Conclusion: We conclude that the addition of magnesium sulphate 50 mg/10 ml saline to epidural bupivacaine/lidocaine provides better postoperative analgesia as well as reducing serum B endorphins in the postoperative period without increasing the incidence of complications in high knee osteotomy orthopedic surgery postoperatively.

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1. Introduction

It has been reported that more than half of postoperative patients receive suboptimal pain control. [1] Surgeons often underestimate the severity and significance of postoperative pain and it could adversely affect clinical outcome and can have significant economic impact. [2] Complications may also be related to the physiologic response to pain and prolonged periods of diminished mobility and these include pulmonary and vascular complications including pneumonia and deep venous thrombosis. Inadequately treated acute pain may ultimately lead to chronic pain via sensitization of the nervous system. [3]

Regional anesthesia is an attractive analgesic modality, which is safe, efficient and of reasonable duration of action. Many studies used different adjuvants with epidural anesthesia that could enhance the duration of regional anesthesia and postoperative pain relief with least complications[4]. Magnesium sulphate has anti-inflammatory, analgesic and opioid-sparing effect is an effective postoperative pain[5]. Its antinociceptive action

seems to be associated with the regulation of intracellular calcium flux, [6,7] or modulation of N-methyl-D-aspartate (NMDA) receptors either peripherally or centrally [8,9]. Prior studies had proven that intrathecally administered magnesium prolonged the duration of action of intrathecal opioid without increasing its side effects[5]. These effects have prompted the investigation of epidural magnesium as an adjuvant for postoperative analgesia [4]. Magnesium has been shown to provide analgesia without complication when administered in the epidural space in combination with bupivacaine[7].

Beta-endorphin is an endogenous morphine-like hormone (opioid) produced primarily in the anterior lobe of the pituitary gland. [9]. Pain, as a stress modality, increases plasma beta endorphin titers by augmenting glucocorticoid release and adrenergic stimulation of the hypothalamus-pituitary axis[10].

The primary function of beta-endorphin is antinociception; indeed, beta-endorphin has been shown to be 20 to 33 times more analgesic than morphine[10]. Beta-endorphin is released during stress and pain, and it exerts its analgesic effect in an inhibitory

action. B-endorphins suppress neuronal action potential of peripheral somatosensory nerves, especially nociceptive nerve fibers. [11,12] There are other studies that showed that beta-endorphin has inhibitory action in visual, acoustic, and olfactory neural transmission. Other possible effects involve loss of libido, enhanced metabolic catatonic state, and suppressed satiety centers [13]. beta-endorphin is resistance and capacitance vessels vasodilator, with the potential to cause orthostatic hypotension. Plasma beta-endorphin production is elevated during physical activity, and it affects various stages of the immune cascade. [14]

The purpose of this study was to detect the possible relationship between epidural magnesium sulphate, postoperative analgesia and serum beta-endorphin levels in high knee osteotomy orthopedic surgery.

2. Methods

After obtaining the approval of the hospital ethical committee, sixty patients of both sexes, aged between 18 and 65 years, 30 in each group (ASA I or II) scheduled for lower limb orthopedic surgeries (high tibial osteotomy) were enrolled in this randomized, double-blinded controlled study between the period of March 2015 to April 2017. Informed consent was obtained from each patient after thoroughly explaining the epidural technique as well as the Numeric rating scale (NRS; 0: no pain; 10: worst pain) and research plan.

All patients were evaluated with respect to hemodynamics including the heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO₂). An epidural catheter was inserted at the L3–L4 or L4–L5 intervertebral space under local anesthetic with the use of loss of resistance technique, and proper position was tested by injection of lidocaine 2% (3 ml).

The study was done in a double-blind method using a sealed envelope technique.

Patients were randomly assigned to one of two equal groups. First group, 30 patients, (control group) received 10 ml saline via epidural catheter followed by injection of saline 2 ml/h during the surgery. Second group, 30 patients, (Mg group) received 50 mg magnesium sulphate (MgSO₄) in 10 ml as an initial bolus dose followed by injection of 10 mg/h (2 ml/h) during the surgery. Epidural bupivacaine 0.5% in a dose of 1 ml/segment and lidocaine 2% in a dose of 1–2 ml/segment was given before the surgery to all patients to achieve block from L4–T8 (9 segments). Sensory block was assessed bilaterally by using loss of sensation to pinprick with a short needle. Assessment of motor block was done using a modified Bromage scale (0: no motor block, 1: inability to raise extended legs, 2: inability to flex knees, 3: inability to flex ankle joints). [14]

3. Primary outcome

Patients' first analgesic requirement times were recorded. The time from end of surgery till the first request of analgesia was defined as the time to the first requirement for postoperative epidural analgesia.

4. Secondary outcome

MAP, HR, and pain score using NRS between 0 and 10 (0 = no pain, 10 = most severe pain) were recorded on arrival to recovery, every hour for 6 h and every 6 h for 24 h in the postoperatively. An NRS of ≤ 4 was considered as acceptable pain control. [15]

Blood samples were drawn to measure serial serum B endorphins (SBE); before placement of the epidural catheter, after complete sensory/motor loss, end of the surgery, every hour for 6 h, then every 6 h for 24 h postoperatively. During the surgery, top ups of epidural bupivacaine 0.5% were given, if needed, to achieve a block up to T8 level. Post-operatively patients discharged to the ward with stable hemodynamic data, fully recovered sensory/motor block, pain-free, and no nausea or vomiting.

Epidural catheter was left in place for 24 h, and used to administer analgesia, if needed, in the form of 5 ml bupivacaine 0.5% boluses, titrated according to the analgesic response or appearance of side-effects. If patients had inadequate analgesia, supplementary rescue analgesia with intramuscular pethidine 50 mg was available. We monitored complications related with the epidural medications Nausea/vomiting, Hypotension, Bradycardia, Respiratory depression. A blinded anesthesiologist who was unaware of the drug given, performed all assessments.

5. Statistical analysis

Sample size was calculated from a previous published data [16] showed that first analgesic request in epidural block for patients undergoing lower limb surgery was 240 minutes, with α error set at 0.05 (two-sided) and 90% for power of the study, the calculated sample size required to detect difference was 48 patients. Another 12 patients were added to the study to compensate for violation of the study protocol.

Data entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation. Chi-square test was used to compare qualitative variables. Mann–Whitney test was used to compare two quantitative variables. Spearman correlation was done to measure correlation between quantitative variables in case of non-parametric data. P-value considered statistically significant when $P \leq 0.05$.

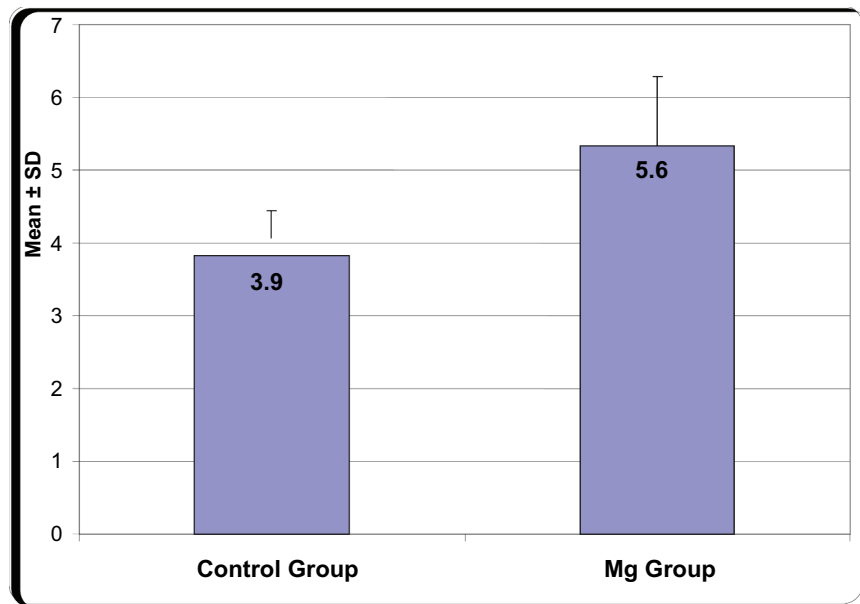


Figure 1. First analgesic requirement time. Values are show as mean \pm standard deviations.

Table 1. Patient characteristics of the studied groups.

	Control Group (n = 30)	Mg Group (n = 30)	P-value
Age (years)	51.77 \pm 5.05	51.03 \pm 3.66	0.433
Sex (male/female)	5/25	11/19	0.08
Weight (kg)	83.46 \pm 12.47	81.19 \pm 11.44	0.476
Height(cm)	159.14 \pm 10.74	161.11 \pm 12.33	0.522
ASA score (I/II)	16/14	12/18	0.301
Duration of surgery (min)	88.06 \pm 5.18	89.83 \pm 4.97	0.195

Data are represented as absolute number or mean \pm SD
P-value < 0.05 is considered significant
ASA (American Society of Anesthesiologists)

6. Results

Patient characteristics showed insignificant differences between the two study groups [Table 1](#). Likewise, pre-operative and intraoperative hemodynamics showed insignificant difference between the 2 study groups, [tables 2](#) and [tables 3](#). However, mean arterial pressure showed significant difference between the two groups at 4 and 6 h postoperatively, [Table 2](#), where, heart rate showed statistical difference at 4, 6, and 18 h postoperative, [Table 3](#). First analgesic requirement time for patients after surgery was significantly longer in Mg group compared to control group ($P < 0.05$) [Figure 1](#), and the frequency of requesting analgesia was significantly less in magnesium group, [Table 5](#).

No patient in the two groups complained of pain during surgery. Whereas the postoperative NRS was significantly less in magnesium group compared to control group at 2, 4 and 6 h postoperatively, [Table 4](#). Serum B-endorphins levels showed statistically significant difference at 2, 4 and 6 h postoperatively, [Table 4](#), being less in magnesium sulphate group. However, baseline (preoperative) and intraoperative serum

Table 2. Mean arterial pressure over the study period (mmHg).

Time	Group	mean	SD	P-value
Baseline (before epidural placement)	Control group	105.00	3.134	0.450
	Mg group	104.40	4.454	
After sensory/motor block	Control group	97.67	3.37	0.432
	Mg group	89.76	3.44	
End of surgery	Control group	98.7	4.2	0.565
	Mg group	102.2	9.4	
An hour post-operative	Control group	106.76	0.54	0.876
	Mg group	99.9	6.4	
Two hours postoperative	Control group	106.3	0.44	0.654
	Mg group	98.87	3.41	
3 hours postoperative	Control group	104.8	1.55	0.432
	Mg group	96.8	2.41	
4 hours postoperative	Control group	133.6	2.1	0.004*
	Mg group	88.25	2.45	
5 hours postoperative	Control group	85.7	3.654	0.435
	Mg group	99.3	1.44	
6 hours postoperative	Control group	124.87	1.75	0.001*
	Mg group	77.3	2.65	
12 hours postoperative	Control group	98.87	2.35	0.654
	Mg group	123.3	2.87	
18 hours postoperative	Control group	100.2	1.9	0.435
	Mg group	98.4	2.765	
24 hours postoperative	Control group	102.6	2.76	0.657
	Mg group	87.3	1.76	

MAP, mean arterial blood pressure. Values are presented in absolute numbers.

B-endorphins showed no statistically significant difference between the studied groups.

Total amount of pethidine in 24 hours was significantly lower in Mg group than in control group As in Mg group, mean was 105 with SD 15.26,

Table 3. Heart rate changes over the study period (beats/min.).

Time	Group	mean	SD	P-value
Baseline (before epidural placement)	Control group	82.67	3.134	0.480
	Mg group	86.21	4.454	
After sensory/motor block	Control group	64.87	3.37	0.632
	Mg group	73.76	3.44	
End of surgery	Control group	83.7	4.2	0.465
	Mg group	86.2	9.4	
An hour post-operative	Control group	79.76	0.54	0.776
	Mg group	75.9	6.4	
Two hours postoperative	Control group	69.3	0.44	0.584
	Mg group	75.87	3.41	
3 hours postoperative	Control group	69.8	1.55	0.332
	Mg group	86.8	2.41	
4 hours postoperative	Control group	89.6	2.1	0.003*
	Mg group	64.25	2.45	
5 hours postoperative	Control group	97.7	3.654	0.435
	Mg group	86.3	1.44	
6 hours postoperative	Control group	89.87	1.75	0.004*
	Mg group	65.3	2.65	
12 hours postoperative	Control group	68.87	2.35	0.454
	Mg group	74.3	2.87	
18 hours postoperative	Control group	87.2	1.9	0.001*
	Mg group	66.4	2.765	
24 hours postoperative	Control group	66.6	2.76	0.987
	Mg group	76.3	1.76	

P value (≤ 0.05) is considered significant. Values are presented in absolute numbers.

Table 4. Pain numerical rating score and serum B endorphin levels over the study period.

Time	NRS/SBE	Control group (n = 30)	Mg group (n = 30)	P value
Baseline (before epidural placement)	NRS	1 \pm 0.8	1 \pm 0.7	≥ 0.05
	SBE	108.50 \pm 3.76	107.64 \pm 4.77	≥ 0.05
After sensory/motor block	NRS	1 \pm 0.34	1 \pm 0.44	≥ 0.05
	SBE	89 \pm 5.4	79 \pm 7.4	≥ 0.05
End of surgery	NRS	1 \pm 0.2	1 \pm 0.3	≥ 0.05
	SBE	112 \pm 5.4	102 \pm 9.4	≥ 0.05
An hour post-operative	NRS	2 \pm 0.76	2 \pm 0.54	≥ 0.05
	SBE	120 \pm 8.4	119 \pm 6.4	≥ 0.05
Two hours postoperative	NRS	4.7 \pm 0.44	1.4 \pm 0.44	0.001*
	SBE	233.38 \pm 36.41	106.38 \pm 36.41	0.002*
3 hours postoperative	NRS	2.7 \pm 0.88	2.9 \pm 0.23	≥ 0.05
	SBE	76.38 \pm 56.41	66.38 \pm 96.41	≥ 0.05
4 hours postoperative	NRS	5.6 \pm 0.32	2.8 \pm 0.44	0.003*
	SBE	243.58 \pm 36.22	111.38 \pm 56.41	0.002*
5 hours postoperative	NRS	3.7 \pm 0.75	3.3 \pm 0.46	≥ 0.05
	SBE	99.3 \pm 3.41	102.8 \pm 26.41	≥ 0.05
6 hours postoperative	NRS	1.3 \pm 0.44	0.3 \pm 0.6	0.001*
	SBE	97.38 \pm 36.41	89.38 \pm 36.41	0.003*
12 hours postoperative	NRS	2.3 \pm 0.65	2.6 \pm 0.75	≥ 0.05
	SBE	123.38 \pm 36.41	109.38 \pm 36.1	≥ 0.05
18 hours postoperative	NRS	1.7 \pm 0.89	1.9 \pm 0.9	≥ 0.05
	SBE	98.38 \pm 45.1	87.38 \pm 76.41	≥ 0.05
24 hours postoperative	NRS	1.6 \pm 0.66	1.8 \pm 0.44	≥ 0.05
	SBE	87.36 \pm 36.1	76.8 \pm 86.41	≥ 0.05

* P value is significant (≤ 0.05), NRS: numerical rating score. SBE: serum B-endorphin. Data presented as mean \pm standard deviation, or absolute number.

Table 5. Post-operative analgesic profile.

	Control Group (n = 30)	Mg Group (n = 30)	P-value
Time of first analgesic request (hours)	3.9 \pm 0.37	5.6 \pm 0.96	0.000*
Number of requests of pethidine (Two/Three)	2/28	3/27	0.000*
Total amount of pethidine (mg)	146.7 \pm 12.7	105.0 \pm 15.3	0.000*

* Statistically significant difference ($p \leq 0.05$)

Values are shown as mean \pm standard deviation.

whereas, in control group mean was 146.67 with SD 12.69, Table 5.

No significant differences were reported regarding the incidence of sedation or side effects between groups, data not show.

7. Discussion

In the present study, we investigated the effect of adding magnesium sulphate as adjuvant to Epidural bupivacaine 0.5% in a dose of 1 ml/segment and lidocaine 2% in a dose of 1–2 ml/segment, on the post-operative pain scores, serum b-endorphins levels and postoperative pain perception. Our study stands out from other studies investigating the role of magnesium sulphate in epidural block as b-endorphins serum levels were estimated along with pain scores in the postoperative period. Plasma BE levels might serve as biomarkers of endogenous antinociceptive capacity. [17]

In line with other studies, [18,19] The results of this study showed that there were insignificant differences between the two groups regarding intraoperative hemodynamics (heart rate, and mean arterial blood pressure). Also, in accordance with other published data, [20] this hemodynamic difference became significant in the postoperative period when patients started regaining somatic sensation.

NRS showed significant reduction the magnesium group in the postoperative period at 2, 4 and 6 hours. This reflects better antinociception control in the magnesium group supported with a statistically significant decrease in the number of patients requesting early postoperative analgesia as well as total pethidine consumption. This in accordance with other studies that showed reduction in both NRS and total opioid consumption in the postoperative period when magnesium sulphate is used in epidural analgesia [21,22]. This Opioid sparing effect was in accordance with other studies done to assess the analgesic effects of adding magnesium sulphate to epidural Bupivacaine in the lower abdominal surgery, [23] combined epidural and intrathecal magnesium sulphate in orthopedic surgeries [24], and continuous intraoperative epidural magnesium sulphate infusion [25]

Plasma BE might act as a biomarker for endogenous opioid analgesic function. [26] In this study there was a statistical difference of BE serum levels being higher in magnesium sulphate group at 2, 4, and 6 h postoperatively. Some studies suggesting that plasma BE levels predict post-operative opioid need and it might also be a marker for more effective endogenous opioid analgesia. Moreover, some clinical researches showed that higher plasma BE predicts greater subsequent acute pain intensity and that higher BE levels could be a marker for enhanced endogenous opioid analgesia. [27,28]

The mechanism of how magnesium exerts its analgesic action is still unclear. A popular theory is that the anti-nociceptive actions is the result of its inhibition of the NMDA receptor. [29] The potentiation of epidural analgesia when magnesium is used as adjuvant has been described in several reports. [30–32] In our study, patients who received magnesium sulphate during the operation showed to have less postoperative pain compared with patients who did not. These observations are in accordance with prior studies results on the analgesia-potentiating effect of magnesium. Nevertheless, there has been a previous report suggesting that the mechanism of magnesium antinociception property might be related to endogenous opioid hyperalgesia. [33,34]

Whether magnesium sulphate could have antinociception action via modulating endogenous opioid analgesia, that beyond the scope of this study and further study is needed to clarify the mechanism of the effect of magnesium on the attention of increased pain intensity.

As regard safety of adding magnesium sulphate to epidural block, this study did not observe significant epidural drugs-related side effects postoperatively. The results in accordance with other studies that have tested the safety of epidural magnesium sulphate in epidural anesthesia. [35]

Our study has potential limitations. First, we did not measure serum b endorphins in the CSF which could reveal another understanding of the pain modulating effect of epidural magnesium sulphate. Second, we did not exclude various pathological states that might have been associated with abnormal endorphin levels e.g., menopausal hormonal changes, as well as migraine and rheumatoid arthritis. Thus, interpreting the results of b-endorphin should be thought of in this context. Finally, we assessed the postoperative rest pain because of the mobility restrictions during the postoperative period. If postoperative pain was evaluated during patient mobility, which could have been considered a stimulus, the results would have been shown magnesium sulphate role in early mobilization, if any.

In summary, we conclude that the addition of magnesium sulphate 50 mg/10 ml saline to epidural bupivacaine/lidocaine provides better postoperative

analgesia as well as reducing serum B endorphins in the postoperative period without increasing the incidence of complications in high knee osteotomy orthopedic surgery postoperatively.

Declaration

The Authors declare that there is no conflict of interest.

Disclosure statement

No potential conflict of interest was reported by the authors.

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