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Research article

Evaluation of effect of intravenous Magnesium Sulfate infusion on tourniquet induced hypertension and pain in arthroscopic knee surgery patients under epidural anesthesia

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KEYWORDS

Tourniquet induced hypertension-epidural;
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Abstract *Objective:* This prospective randomized, double blind controlled study was designed to evaluate the effect of Intravenous (i.v) magnesium sulfate infusion on attenuation of tourniquet induced hypertension (TIH) and tourniquet pain and also its effect on postoperative analgesia in patients undergoing arthroscopic knee surgery under epidural anesthesia.

Patients and methods: Seventy ASA I and II patients were scheduled for arthroscopic knee surgery with tourniquet under epidural anesthesia. Patients were allocated randomly into two equal groups ($n = 35$): Magnesium (Mg group) received a bolus dose of IV magnesium sulfate 30 mg/kg in 50 ml saline over 10 min, followed by infusion 10 mg/kg/h and control group received iv saline. Systolic and Diastolic blood pressure (SBP, DBP) and Heart rate (HR) were measured at baseline (before anesthesia), after epidural anesthesia, then every 10 min after the tourniquet inflation, and 1, 5, 10, and 30 min after deflation with recording incidence of (TIH), tourniquet pain, and total iv fentanyl consumption (was given iv 1 ug/kg with tourniquet pain); postoperative Visual Analogue Scale (VAS) score was assessed at 1, 2, 4, 8, 12, 18, and 24 h, postoperative pethidine consumption (given iv 0.5 mg/kg if VAS > 3) was recorded, and serum magnesium was measured preoperatively and at 6 and 24 h postoperatively.

Results: SBP, DBP and HR were significantly higher in the control group than in the Mg group ($p < 0.001$) after 50 min of inflation. The number of patients who developed TIH and tourniquet pain was significantly lower in Mg group compared to control group 3(8.57%) vs 12(34.28%) ($p < 0.05$), with significantly shorter time to feel pain in control group 48 ± 8 min versus 71 ± 7 min ($p < 0.001$). Intraoperative fentanyl requirements were significantly higher in control group compared to Mg group ($p < 0.001$). Mg group had significantly lower postoperative VAS scores and pethidine consumption ($p < 0.001$) and significantly longer time to first request of

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postoperative analgesia compared to control group ($p < 0.001$). Postoperative serum magnesium was significantly higher in Mg group at 6 h postoperative ($p < 0.001$).

Conclusion: In patients undergoing arthroscopic knee surgery under epidural anesthesia, IV magnesium sulfate in a dose of 30 mg/kg, followed by 10 mg/kg/h infused before tourniquet inflation could reduce TIH, and tourniquet pain with reduction in intraoperative IV fentanyl and postoperative pethidine requirements.

1. Introduction

Management of patients undergoing surgery with tourniquet application as joint replacement or other lower limb surgery becomes challenging during general or regional anesthesia. Although pneumatic tourniquet may be helpful to decrease intraoperative bleeding and maintain dry surgical field, on the other hand this is associated with some side effects that occur during inflation as well as after deflation [1]. The most common complication after tourniquet inflation is tourniquet pain which initiates tourniquet-induced hypertension (TIH). Also marked hypotension can occur after tourniquet deflation due to redistribution of the circulating blood back into the limb and post-ischemic reactive hyperemia with release of accumulated metabolites into the circulation leading to hypotension and metabolic changes [2].

With prolonged tourniquet inflation during general anesthesia patients may develop hypertension and tachycardia that may be due to activation of the sympathetic nervous system in response to pain which is difficult to relief by narcotics and different analgesics. Patients under regional anesthesia complain of extreme discomfort from prolonged tourniquet inflation [3]. The tourniquet pain, is described as severe, dull, aching sensation at the site of the tourniquet application, and it can develop despite adequate anesthesia and analgesia during surgery. It is difficult to treat tourniquet pain and hypertension (TIH) [4].

Tourniquet-induced hypertension (TIH) is generally defined as a progressive increase of more than 30% of systolic blood pressure that may be observed 30–60 min after tourniquet inflation; the exact mechanism of its development is unknown but most probably related to tourniquet pain [5]. It is thought that prolonged firing of unmyelinated slow-conducting c-fibers is most probably responsible for tourniquet-induced pain and hypertension due to release of glutamate which acts on N-methyl-D-aspartic acid (NMDA) receptors in the spinal cord [6].

Various NMDA receptor antagonists were used to manage tourniquet pain and TIH [5,7–9]. Other drugs and methods were used to reduce tourniquet effects such as the use of regional anesthesia, intravenous (IV) opioids, paracetamol, gabapentin, non-steroidal anti-inflammatory drugs (NSAIDs), melatonin and clonidine which has been reported to depress nerve action potentials in c-fibers [10].

Regional anesthetic techniques are most commonly used for orthopedic surgery as they are safe, effective and can provide prolonged postoperative analgesia [11].

Magnesium sulfate is a NMDA receptor antagonist, and it has antinociceptive effects that had been estimated in animal and human models of pain [12]. Some studies assessed the analgesic effect of magnesium sulfate with general anesthesia and proved to be effective in lowering intraoperative anesthetic and analgesic requirements as well as postoperative requirements of opioid analgesics [12,13]. Few studies have evaluated the effect of magnesium sulfate infusion during regional anesthesia [14,15].

The aim of this prospective randomized, placebo-controlled, double blind study was to evaluate the efficacy of IV magnesium sulfate infusion for attenuation of tourniquet induced hypertension (TIH) and tourniquet pain as well as its effect on postoperative analgesia in patients undergoing arthroscopic knee surgery under epidural anesthesia.

2. Patients and methods

This prospective randomized, double-blind, placebo-controlled study was conducted at the Department of Orthopedic Surgery in Kaser El Aini Hospital from October 2014 to October 2015. After obtaining institutional ethical committee approval and an informed written consent was signed by each patient included in the study, the study started and involved 70 patients aged 20–60 years of American Society of Anesthesiology (ASA) class I or II of both sexes who were undergoing arthroscopic knee surgery requiring thigh tourniquet for at least one hour under epidural anesthesia.

Exclusion criteria were patients with known hypersensitivity to local anesthetics, local infection in the lumbar region, bleeding diathesis, a history of hypertension, renal, hepatic, respiratory or cardiac diseases and varying degree of heart block, as well as neurologic, neuromuscular or psychiatric diseases. Also patients with history of allergy to the study drug, and patients treated with calcium channel blockers or magnesium were not included in the study.

Prior to surgery, patients had a full explanation of the epidural technique as well as the visual analogue scale (VAS; 0: no pain; 10: worst pain), the method of postoperative analgesia and to demand rescue analgesic at the onset of breakthrough pain (VAS > 3).

Patients were randomly assigned to two equal groups (35 patients in each group). Randomization was done using computer-generated number table of random numbers and conducted using sequentially numbered, opaque and sealed envelope (SNOSE). The two groups were as follows:

- Magnesium group (Mg group) ($n = 35$): received IV magnesium sulfate bolus dose of 30 mg/kg in 50 ml saline over 10 min, followed by iv infusion of 10 mg/kg/h in 100 ml saline before tourniquet inflation and the iv infusion continued throughout surgery. Magnesium infusion stopped at the onset of tourniquet deflation.

– Control group ($n = 35$): received iv 50 ml saline over 10 min, followed by iv saline infusion (the same volume as Mg group) continued throughout surgery and stopped at the onset of tourniquet deflation.

The patients, investigators, anesthesiologists and the surgeons were blinded to the given infusion. The infusions were prepared preoperatively by an anesthesiologist unaware of group assignments using identical 100-mL infusion syringe pump. Standard protocol was followed for all patients throughout the study.

In the operation theater intravenous (i.v) access with 18G cannula was established and preloading with Ringer Lactate was carried out standard monitoring including the following: Electrocardiogram (ECG), pulse oximetry and noninvasive arterial blood pressure monitors were applied, and a baseline heart rate, blood pressure (systolic, diastolic) and peripheral oxygen saturation were recorded. Each patient received 10 ml/kg lactated Ringer's solution at body temperature as fluid preload over approximately 20–30 min before epidural and 6–8 ml/kg/h after epidural anesthesia throughout surgery.

Another intravenous access was established using 18-gauge cannula and infusion of the study drugs was given as the following: before the insertion of epidural catheter, the patients in the first group (magnesium group) received IV magnesium sulfate bolus dose of 30 mg/kg in 50 ml saline over 10 min via a syringe infusion pump, followed by iv infusion of 10 mg/kg/h in 100 ml saline (started after the insertion of epidural catheter), and the second group (control group) received iv 50 ml saline over 10 min (before the insertion of epidural catheter), followed by iv saline infusion (the same volume as Mg group) (started after the insertion of epidural catheter), Magnesium or saline iv infusion stopped at the onset of tourniquet deflation.

Patients of both groups received epidural anesthesia under complete aseptic conditions. The epidural space was identified at the level of L3-L4 or L4-L5 interspace with 18 gauge Tuohy needle. The needle was inserted with the aperture directed cephalad. The epidural space was defined by loss of resistance technique using saline and correct position was confirmed by injection of lidocaine 2% (3 ml) with epinephrine in concentration of 1:200,000. The epidural catheter 20 G was inserted, advanced 3–5 cm into the epidural space and proper fixation and confirmation of its position were performed after negative aspiration of CSF and blood to rule out accidental intrathecal or intravascular placement. All patients received 0.5% Bupivacaine, 1 ml/segment was given in the epidural catheter incrementally over 5 min period and the patient was repositioned supine. Sensory block was assessed by using loss of temperature sensation with an ice cube every 5 min for first 30 min. The level to be blocked was up to T10, and an additional 5 mL of local anesthetic added after 10 min if the block height was below T10.

Motor block was evaluated using a modified Bromage scale [16] (0: no motor block, 1: inability to raise extended legs, 2: inability to flex knees, 3: inability to flex ankle joints).

The pneumatic tourniquet inflated after epidural anesthesia (when sensory level was fixed at T10 and modified Bromage score of 3), and it was placed on the affected lower limb over a cotton layer after elevation of the limb; then, exsanguination was done using crepe bandage. The pneumatic tourniquet inflation pressure was 300 mmHg. After tourniquet inflation the operation started. At the end of operation just before releasing the tourniquet, a 200-mL bolus of lactated Ringer's solution was infused rapidly.

During the study period arterial blood pressure (SBP, DBP), heart rate (HR), and oxygen saturation were monitored continuously and recorded at the following time points: upon arrival to operating room before anesthesia and before starting infusion of the study drug (baseline), and after epidural anesthesia and then every 10 min after tourniquet inflation and at 1, 5, 10 and 30 min after tourniquet deflation. The number of patients who developed TIH (which is defined by an increase in SBP > 30% of the baseline value) was also recorded.

Assessment of intraoperative pain scores was made on the basis of the visual analogue scale (VAS) measured every 20 min after tourniquet inflation till 5 min after deflation. When patients complained of pain during surgery, he was asked to describe the nature of that pain it was recorded as tourniquet pain if it was not related to the surgical field and was described as a dull, tight, aching sensation at the area of the tourniquet application. At the onset of tourniquet pain, 1 μg/kg of intravenous (iv) fentanyl was given if VAS > 3, with recording the total iv fentanyl consumption, the onset time of pain, and the level of sensory block was assessed by pin prick method by an observer unaware of the patient's group.

In both groups any hemodynamic changes were recorded: hypotension defined as SBP < 90 mmHg or > 20% decreases in baseline values, and it was treated with a bolus of 200 mL of Lactated Ringer's solution. If hypotension persisted for > 5 min, 5 mg ephedrine was given intravenously. Bradycardia defined as heart rate < 50 beat/min was treated with 0.3 mg IV atropine (can be repeated if required). Tachycardia was defined as heart rate > 100 or HR > 20% of the baseline value, and TIH was defined as increase in SBP > 30% of the baseline value. Iv fentanyl 1 μg/kg was given to manage TIH with recording of number of patients who developed TIH and the total amount of fentanyl was given intraoperatively. If there was no response iv esmolol 25 mg increments were given.

The epidural catheter was removed at the end of surgery, diclofenac sodium 75 mg intramuscularly was given, and patients were transferred to the post anesthesia care unit (PACU) with continuous assessment of BP, HR, SPO_2, VAS and any side effects (nausea, vomiting, and shivering). Rescue medication was administered after any untoward event. Respiratory depression (respiratory rate < 9/min or SpO_2 < 92%) was treated by supplemental oxygen. Heart rate < 50 bpm was controlled by 0.3 mg IV atropine, and nausea and vomiting were treated with 4 mg IV ondansetron. Postoperative sedation was monitored and recorded at PACU by using a 4-point rating scale [17] (Grade 0: awake and alert; 1: mildly sedated, easily aroused; 2: moderately sedated, aroused by shaking; 3: deeply sedated, difficult to be aroused by physical stimulation). All assessments were carried out by another anesthesiologist not involved in the intraoperative care of the patients and blinded to the group assignment.

Patients were discharged to the ward when all hemodynamic variables were stable with completely resolved motor block, satisfactory pain relief (VAS < 3), and the absence of nausea and vomiting.

The postoperative pain was assessed by VAS at 1, 2, 4, 8, 12, 18 and 24 h after surgery. Postoperative analgesia was

provided by Pethidine 0.5 mg/kg IV if VAS > 3 or if the patient complained of pain and asked for analgesia in between VAS assessment visits considering at least 4 h after the last dose. The time for the first analgesic requirement and the total pethidine consumption in the first 24 h were recorded.

Serum Magnesium level was assessed before magnesium infusion (baseline) and then at 6 and 24 h postoperatively.

Primary outcome measure of the study was to assess the incidence of TIH in both groups.

Secondary outcome measures were to assess frequency of tourniquet pain, onset of tourniquet pain, total iv fentanyl consumption, postoperative VAS, the duration of effective analgesia (the time interval between the end of study drug infusion and the first request for analgesic), total pethidine consumption and postoperative complaints (nausea, vomiting, respiratory depression, and shivering). Also the preoperative and postoperative serum magnesium was assessed.

2.1. Statistical analysis

The required sample size was calculated using IBM© SPSS© SamplePower© (IBM© Corp., Armonk, New York, USA). Based on previous study with detection of a reduction in incidence of TIH from 62.9% to 22.2% [18] and with the power set at 80% and α error level fixed at 0.05, it was estimated that a sample of 28 patients in each group is required to detect significant decrease in incidence of TIH. The sample size was increased to 35 patients in each group enrolled to compensate for any dropouts during the study. Data were described in terms of mean ± standard deviation (±SD) or frequencies and percentages as appropriate. Comparison of numerical variables between the two groups was done using *Student t* test for independent samples for normally distributed data and Mann Whitney-*U* test if data are not normally distributed. For comparing categorical data, Chi square (or Fisher's exact) test was used. A p value < 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15.

3. Results

Fig. 1 shows the CONSORT diagram for the flow of participants through each stage of the present study.

There were no significant differences between the two groups with respect to patients' characteristics, duration of

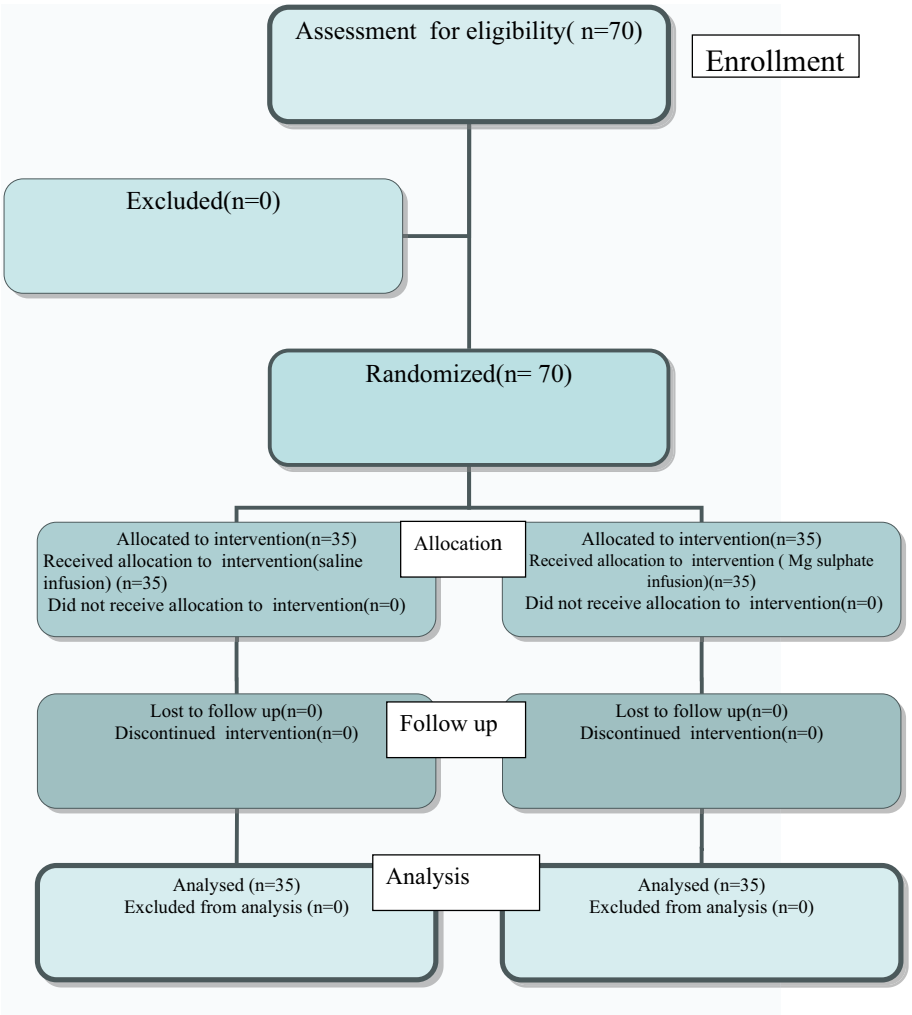

Figure 1 CONSORT diagram showing the flow of participants through each stage of the study.

surgery, tourniquet time and baseline hemodynamic variables ($p > 0.05$) (Table 1).

The two groups were similar in the maximal dermatome height achieved (T8-10). No difference in the quality of sensory and motor block before and during surgery was noted between groups (the pneumatic tourniquet inflated after epidural anesthesia when sensory level fixed at T10 and Bromage score of 3). There was no statistical significant difference between both groups for their mean time required to achieve complete sensory block up to the level of T-10 (10.59 ± 2.87 min in magnesium group versus 10.47 ± 2.93 min in the control group), and time of motor block to Bromage Score-3 (19.39 ± 2.87 min in magnesium group versus 20.45 ± 2.34 min in control group) ($p > 0.05$).

Systolic and diastolic blood pressure values were comparable in both groups at the baseline, after epidural induction of anesthesia and after tourniquet inflation (Ti10-Ti40), but there was significant increase in SBP and DBP in the control group compared to baseline value and to Mg group values at Ti50, Ti60, Ti70 and Ti80 ($p < 0.001$). After tourniquet deflation there was significant reduction in mean SBP and DBP from baseline values in both groups in the 1st and 5th min after deflation (Td1 and Td5) ($p < 0.001$) but both groups return to baseline values at 10 and 30 min (Td10 and Td30) (Figs. 2 and 3).

Significantly fewer patients that had TIH were observed in Mg group compared to control group (3(8.57%) vs 12 (34.28%); ($p < 0.05$)). The number of patients required esmolol was more in control group compared to Mg group (4 patients (11.42%) vs 1 patient (2.85%)) but there was no statistically significant difference between both groups ($p > 0.05$).

Heart rate (HR) significantly increased in control group compared to baseline value and to Mg group measurements from Ti60, Ti70 and Ti80 ($p < 0.001$). After tourniquet deflation there was comparable significant increase from baseline values of HR in both groups in the 1st and 5th min after deflation (Td1 and Td5) but both groups return to near baseline values at 10 and 30 min (Td10 and Td30) Fig. 4.

The SpO_2 was higher than 95% in all patients of the two groups, either during surgery or in the PACU.

VAS scores for tourniquet pain were significantly lower in Mg group at 40, 60 and 80 min after tourniquet inflation and 5 min after deflation (Table 2). Significantly fewer patients complaining of tourniquet pain were observed in Mg group compared to control group (3(8.57%) vs 12(34.28%); $p < 0.05$), with significantly shorter time to feel pain in the control group ($p < 0.001$). The total dose of intraoperative iv fentanyl was significantly higher in control group compared to Mg group (148 ± 12 vs. 74 ± 10; $p < 0.001$) (Table 2). The level of sensory block at the onset of tourniquet pain was comparable in the two groups (T-10).

During the postoperative period, Mg group patients had significantly lower VAS scores after 1, 2, 4, 8, and 12 h ($p < 0.001$). After 18 and 24 h VAS scores were comparable (Fig. 5). Time to first request of postoperative analgesia was significantly longer in Mg group compared to control group (243 ± 20 min vs 150 ± 22 min) ($p < 0.001$). The cumulative dose of rescue analgesia (Pethidine) used in the postoperative 24 h was significantly lower in Mg group ($p < 0.001$) (Table 3).

No major complications were seen throughout the study period and no patient needed any intervention due to perioperative respiratory problems. The frequency of postoperative nausea and vomiting and sedation was comparable in both

Table 1 Patient's demographic and operative data.

Variables	Magnesium group $n = 35$	Control group $n = 35$
Age (yrs)	44 ± 5	44 ± 6
Male/female (n)	19/16	17/18
Weight (kg)	70 ± 9	70 ± 8
Height (cm)	161 ± 6	163 ± 6
ASA (I/II)	14/21	16/19
Duration of surgery (min)	118 ± 7	119 ± 7
Duration of Tourniquet (min)	80 ± 8	80 ± 9
Baseline SBP (mmHg)	123 ± 8	122 ± 7
Baseline DBP (mmHg)	75 ± 7	76 ± 7
Baseline HR (beat/min)	78 ± 7	76 ± 7

Data are mean ± SD or numbers.
No statistically significant differences between the two groups.

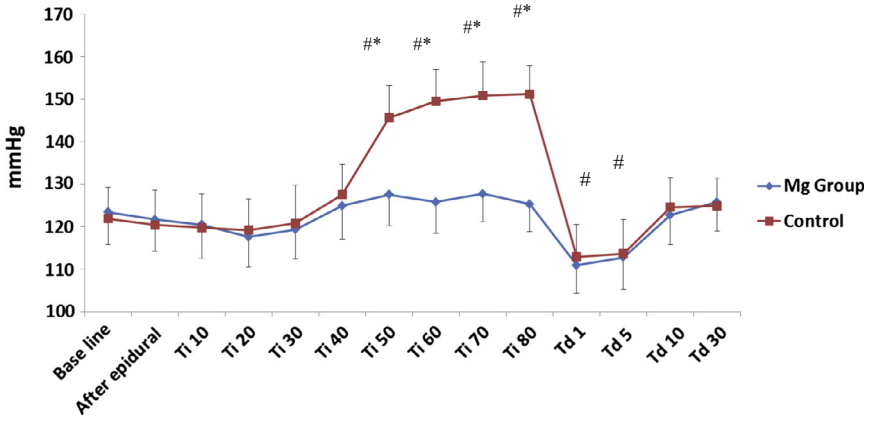

Figure 2 Mean ± SD systolic blood pressure changes (mmHg) over the study period in the studied groups ($n = 35$ in each group) (Mg group = Magnesium group). Ti: min. after tourniquet inflation, Td: min. after tourniquet deflation. *Significant difference between the two groups ($p < 0.001$). #$p < 0.001$ compared to the baseline value in both groups.

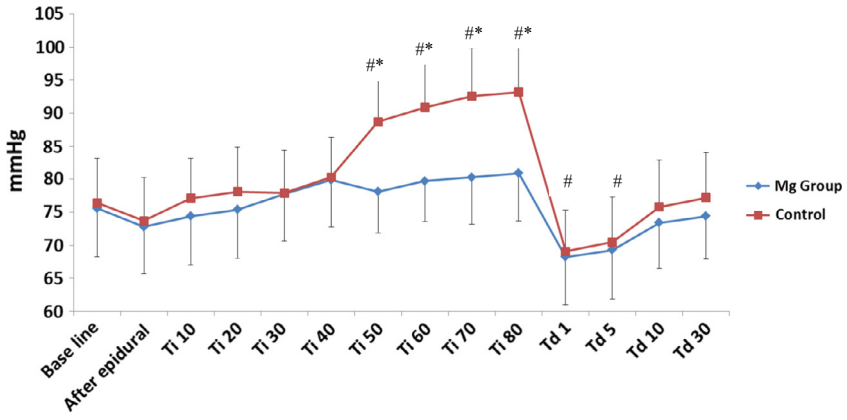

Figure 3 Mean ± SD of diastolic blood pressure changes (mmHg) over the study period in the studied groups (n = 35 in each group) (Mg group = Magnesium group). Ti: min. after tourniquet inflation, Td: min. after tourniquet deflation. *Significant difference between the two groups ($p < 0.001$). #$p < 0.001$ compared to the baseline value in both groups.

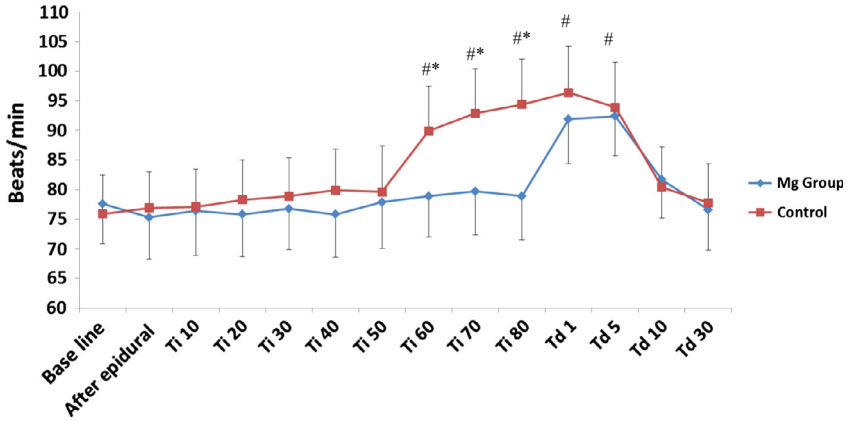

Figure 4 Mean ± SD of heart rate changes (beats/min) over the study period in the studied groups (n = 35 in each group) (Mg group = Magnesium group). Ti: min. after tourniquet inflation, Td: min. after tourniquet deflation. *Significant difference between the two groups ($p < 0.001$). #$p < 0.001$ compared to the baseline value in both groups.

groups, but Mg group had significantly lower frequency of shivering (2.85% vs 28.57%) ($p < 0.01$) (Table 4).

Postoperative serum magnesium was significantly higher in Mg group at 6 h postoperatively ($p < 0.001$) and returned to the normal values at 24 h ($p = 0.224$) (Table 5).

4. Discussion

This study showed that IV magnesium sulfate bolus dose (30 mg/kg), followed by (10 mg/kg/h) infusion before tourniquet inflation during knee surgery under epidural anesthesia could decrease tourniquet-induced hypertension (TIH), and lowered the frequency of tourniquet pain. Also postoperative pain and analgesic consumption were reduced.

The exact mechanism of TIH is not clear but few theories exist explaining the mechanism of TIH and tourniquet pain. One of them suggested that the sympathetic activation due to pain is the cause of TIH [4,7]. The other theory suggested that the unmyelinated, slow C-fibers that are normally inhibited by large, fast, myelinated A fibers mediate this pain causing hypertension [5].

Approximately 30 min after tourniquet inflation, A-delta fibers are thought to be blocked before the C-fibers which lead to loss of conduction in these large A-delta fibers and this seems to take away the post-synaptic inhibition of C-fibers by the large fibers. The skin under the inflated tourniquet provides the continuous stimulation of these C-fibers [6]. Continuous firing of C-fiber nociceptors causes activation of NMDA receptors in the dorsal horn of the spinal cord leading to central sensitization. Associated increases in arterial pressure and heart rate are considered as humoral responses to the pain [5,6,19]. TIH is difficult to be managed by antihypertensive drugs but it subsides immediately after tourniquet deflation [5].

Some studies indicated that the NMDA receptor activation produced increases in mean arterial pressure while the NMDA receptor antagonism blocked the cardiovascular response in animals [20].

Some NMDA receptor antagonists could attenuate tourniquet-induced pain and hypertension under general anesthesia as reported in previous studies [5,8,9,21] as the NMDA receptor antagonists could prevent central sensitization that occurs due to peripheral nociceptive stimulation [19]. Tourniquet pain may occur during spinal or epidural anesthesia

Table 2 Intraoperative characteristics of tourniquet pain in the studied groups.

	Magnesium group $n = 35$	Control group $n = 35$
VAS score after inflation		
20 min	1 (0–1)	1 (0–1)
40 min	1 (0–1)**	2 (0–3)
60 min	1 (0–2)**	3 (1–4)
80 min	2 (1–3)**	3 (2–5)
VAS score 5 min after deflation	1 (0–1)**	2 (1–3)
Number of patients with tourniquet pain	3 (8.57%)*	12 (34.28%)
Onset of tourniquet pain (min)	71 ± 7**	48 ± 8
Total fentanyl requirement (μg)	74 ± 10**	148 ± 12

P value < 0.05 is statistically significant.
* P value < 0.05 in the Magnesium group compared to the control group.
** P value < 0.001 in the Magnesium group compared to the control group.

Table 3 Postoperative analgesic characteristics in the studied groups.

	Magnesium group $n = 35$	Control group $n = 35$
Total dose of pethidine in 24 h (mg)	96 ± 38**	143 ± 48
Time of first dose of pethidine required (min)	243 ± 20**	150 ± 22

Data are mean ± SD.
P value < 0.05 is statistically significant.
** P value < 0.001 in the Magnesium group compared to the control group.

Table 4 Frequency of postoperative side effects in the studied groups.

Side effect	Magnesium group $n = 35$	Control group $n = 35$
Nausea and vomiting	1 (2.85%)	2 (5.71%)
Sedation	2 (5.71%)	1 (2.85%)
Shivering	1 (2.85%)**	10 (28.57%)

Data are numbers of patients (%).
P value < 0.05 is statistically significant.
** P value < 0.01 in the Magnesium group compared to the control group.

despite adequate sensory block, and its occurrence is more frequently observed during epidural anesthesia than spinal anesthesia [4]. It was necessary to evaluate the effect of IV NMDA receptor antagonists in surgery with tourniquet under epidural anesthesia.

In the current study using Mg sulfate infusion before inflation of tourniquet and continued until tourniquet deflation (in arthroscopic knee surgery under epidural anesthesia) could attenuate the hemodynamic response to tourniquet, and the incidence of TIH reduced from 34.28% in the control group to 8.57% in Mg group, and there was more stable intraoperative hemodynamics (SBP, DBP and HR) in most of patients of Mg group during the maintenance of tourniquet inflation, while SBP and DBP increased significantly in the control group from 50 to 80 min ($p < 0.001$) and HR increased significantly from 60 to 80 min after tourniquet inflation ($p < 0.001$). As the mechanism of NMDA receptor antagonism is the same in all NMDA receptor antagonists a study by Yamashita and colleagues [21] showed that preoperative oral dextromethorphan reduced the increase in arterial blood pressure and heart rate during tourniquet inflation. Also Park and colleagues [5] evaluated in their study -(on ketamine which is NMDA receptor antagonist)- the effectiveness of preoperative intravenous ketamine (0.1 mg/kg) to attenuate tourniquet induced hypertension during inflation under general anesthesia and proved that it was effective (28.6% in control group vs 7.1% in ketamine group). In another study conducted by Satsumae et al. [8] it was detected that magnesium sulfate reduced the tourniquet pain and hypertension in healthy volunteers. All these findings proved that NMDA receptor antagonists could attenuate TIH.

Tourniquet deflation was associated with a comparable significant reduction in mean SBP and DBP from baseline in both

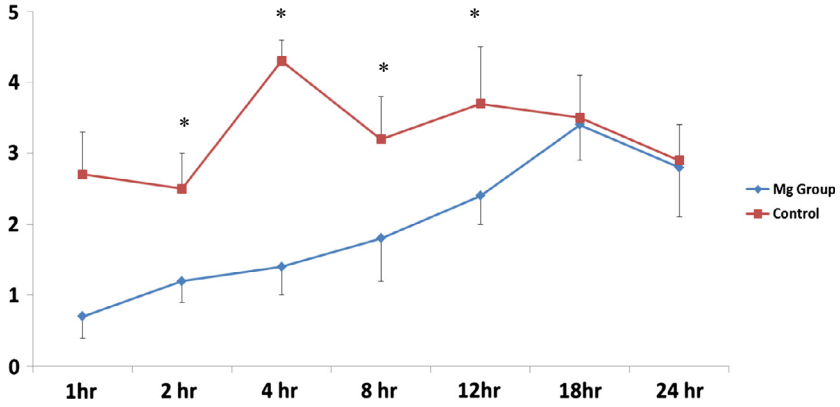

Figure 5 Mean ± SD of VAS score during the first postoperative 24 h in the studied groups ($n = 35$ in each group) (Mg group = Magnesium group). *$p < 0.001$ in Mg group compared to the control group.

Table 5 Postoperative serum magnesium level (mmol/L) in the studied groups.

	Magnesium group $n = 35$	Control group $n = 35$
Baseline (preoperative)	1.22 ± 0.14	1.25 ± 0.12
6 h postoperative	1.74 ± 0.16**	1.09 ± 0.14
24 h postoperative	1.19 ± 0.18	1.14 ± 0.16

Data are mean ± SD.
P value < 0.05 is statistically significant.
** P value < 0.001 in the Magnesium group compared to the control group.

groups with increased HR at 1 and 5 min after deflation but almost returned to the basal level at 10 and 30 min and no serious complications were observed due to the hypotension. Abraham et al's [2] study was in agreement with the current study as they found a significant decrease in both systolic and diastolic blood pressures approximately in the first three minutes after tourniquet release. These changes may be due to decrease in peripheral resistance caused by post ischemic reactive hyperemia in the affected limb. Also Iwama et al. [22] reported heart rate increase and blood pressure fall after tourniquet deflation with combined epidural and propofol anesthesia with preservation of spontaneous respiration.

As regards the onset of tourniquet pain, it was more prolonged in Mg group (71 ± 7 min) than in control group (48 ± 8 min) with lower VAS score and intraoperative fentanyl requirements in Mg group ($p < 0.001$). As the mechanism of NMDA receptor antagonism is the same, a previous study by Viscomi and co workers [23] demonstrated that another one of NMDA receptor antagonists (ketamine) used as an adjuvant in lidocaine-based intravenous regional anesthesia (IVRA) could delay the onset of tourniquet pain. Also Satsumae et al. [8] proved prolonged onset of tourniquet pain with lower pain scores in Mg group compared to control group during tourniquet inflation in healthy awake volunteers. The results of the current study indicate that the frequency of tourniquet pain is not related to the level of sensory anesthesia as the level of sensory block at the onset of tourniquet pain was comparable in the two groups, and this was in line with previous study detected occurence of tourniquet pain in spite of high sensory level [4].

As regards the postoperative analgesic effect of magnesium sulfate the current study demonstrated that preoperative iv magnesium infusion applied before tourniquet inflation significantly decreased postoperative VAS score, prolonged the time to the first analgesic request and reduced the postoperative pethidine requirements. This may be due to potentiation of the analgesic action of pethidine by magnesium through NMDA receptor blockade. These findings of the current study are in line with the reports of previous studies where magnesium was used as a possible adjuvant for intra- and postoperative analgesia [13,14]. Dabbagh et al. [14] observed that magnesium sulfate can serve as a supplementary analgesic providing significant reduction in postoperative pain scores with less postoperative morphine consumption in patients undergoing orthopedic surgery under spinal anesthesia. Other studies [13,24,25] reported the effectiveness of magnesium sulfate in postoperative pain relief after orthopedic, and other types of surgery where magnesium was supplied as continuous infusion or repeated boluses. The results of the current study support the previous studies which evaluated the effect of i.v infusion of magnesium sulfate during spinal anesthesia on postoperative pain. Kahraman and Eroglu [26] reported that the use of i.v magnesium sulfate infusion during abdominal hysterectomy (under spinal anesthesia) where 20 female patients received magnesium sulfate 65 mg kg^{-1} iv infusion in 250 mL 5% dextrose at 3.5 mL/min rate, while the control group (Group C, $n = 20$) received at the same volume of saline during operation in a double-blind randomized manner, the VAS scores were lower in Group M than those in Group C postoperatively ($P < 0.01$). Also, Agrawal et al. [27] concluded that the use of intravenous magnesium with spinal anesthesia reduces post-operative pain and analgesic consumption in patients scheduled for elective orthopedic fixation of fracture of long bones of lower limbs under spinal anesthesia with an infusion of (iv) magnesium sulfate 50 mg/kg/h over 15 min followed by 15 mg/kg/h until the end of the surgery (Group M) and 15 ml of Normal Saline over 15 min followed by 100 ml/h until the end of surgery (Group S). Need for first analgesic requirement was after 262.88 ± 21.11 min in group M and 193.25 ± 17.74 min in the group S ($P = 0.000$). Mean dosage of tramadol needed in first 24 h was less in group M (190 ± 30.38 mg vs. 265 ± 48.30 mg, $P = 0.000$).

Also in a recent study by Taheri and co workers [28] magnesium sulfate 50 mg kg^{-1} in 100 mL of normal saline solution i.v was given as single-dose, just 15 min before induction of anesthesia whereas patients in control group received 100 mL of 0.9% sodium chloride solution at the same time, and they detected that postoperative pain score was lower in magnesium group at 6, 12, and 24 h after the operations significantly. Pethidine requirement was significantly lower in magnesium group throughout 24 h after the surgeries and this is in agreement with the current study. The same results were found in the study by Agrawal et al. [29] who evaluated the effect of i.v infusion of magnesium sulfate during spinal anesthesia, for postoperative pain relief in patients undergoing lower segment cesarean section. Also the study by Sousa et al. [30] proved that intraoperative magnesium sulfate improves postoperative pain control, acting as an opioid-sparing adjuvant.

On the other hand some researchers reported contradictory results; they detected no benefit of pre-treatment with IV magnesium sulfate on decreasing post-operative pain and analgesic consumption after abdominal hysterectomy and cesarean section, and the precise reasons for this discrepancy are unknown [31,32].

The mechanism of the postoperative analgesic effect of magnesium is not clear, but interference with calcium channels and NMDA receptors seems to play an important role. The analgesic action of calcium channel blockers could be mediated by an increase in the nociceptive threshold resulting from interference with calcium influx because calcium is important for the release of neurotransmitters and other substances shared in nociception and inflammation [24].

Magnesium causes a dose-dependent negative inotropic effect, and in humans hemodynamic studies have shown that it has a peripheral (predominantly arteriolar) vasodilatory effect. After rapid infusion of 3 or 4 g of magnesium sulfate, systolic arterial pressure decreased in relation to decreased

systemic vascular resistance [15]. In the present study, considering the negative inotropic effect of Mg, prehydration with 10 ml/kg of lactated Ringer's solution was performed and the Mg bolus dose was infused over 10 min, which is probably why no significant hypotension was encountered after administering the Mg bolus dose. The dose selected in the current study, significantly reduced pain without an episode of severe hypotension and bradycardia. This finding best correlates with results of Ozcan et al's study [33] on patients undergoing thoracotomy. On the other hand El-Sharnouby and El-Sharnouby [34] used magnesium sulfate 40 mg/kg over a period of 15 min before induction and 15 mg/kg/h by continuous intraoperative infusion, and they noticed more episodes of severe hypotension may be related to the higher dose they used.

In the present study, Mg group showed significantly lower frequency of postoperative shivering (1 vs. 10). This finding was consistent with the results of the study done by Wadhwa and colleagues [35] who suggested that magnesium sulfate infusion reduces the shivering threshold in humans. Shivering increases discomfort and worsens postoperative pain, so reduction in shivering may decrease postoperative pain with higher patients' satisfaction [35].

After surgery, patients in the magnesium group showed higher serum Mg concentrations after postoperative 6 h but it returned to the basal level at 24 h. Magnesium toxicity always appears at serum concentration of 2.5–5 mmol/liter [36] which is much higher than the level detected in Mg group in this study (1.74 ± 0.16 mmol/liter).

Ko and colleagues [31] have demonstrated an inverse relation between cerebrospinal fluid (CSF) magnesium concentration and cumulative postoperative analgesic consumption. It is suggested that the detected decrease in pain intensity or in morphine consumption in many previous studies was not due to a direct analgesic effect of magnesium but rather to the prevention of hypomagnesemia which leads to prevention of subsequent NMDA receptor activation [37].

The limitation of this study was the small sample size, and the level of magnesium in CSF was not measured. Also postoperative pain VAS was not assessed with movement.

Further studies are needed to be performed involving cardiovascular disease patients, as TIH caused by tourniquet pain represents a risk factor in patients with pre-existing essential hypertension, ischemic cardiac disease and magnesium sulfate may be useful in these patients. More studies should also be done to evaluate the effect of spinal or epidural magnesium sulfate on tourniquet pain and TIH.

5. Conclusion

In patients undergoing arthroscopic knee surgery under epidural anesthesia, IV magnesium sulfate in a dose of 30 mg/kg, followed by 10 mg/kg/h infused intra-operatively before tourniquet inflation compared to a control group could reduce TIH, and tourniquet pain, postoperative pain with reduction in intraoperative IV fentanyl and postoperative iv pethidine requirements.

Conflict of interest

The authors declare that there is no conflict of interest.

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