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Research Article

# Magnesium sulfate in femoral nerve block, does postoperative analgesia differ? A comparative study

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**Abstract** *Background:* N-methyl-D-aspartate (NMDA) receptors play a major role in central nociceptive transmission. Recent studies identified NMDA receptors peripherally. Magnesium (Mg) has antinociceptive effects due to its antagonistic effect of NMDA receptors. The aim of this randomized, double-blinded, placebo-controlled study was to assess the potential analgesic effect of Mg when directly applied on the peripheral nerves, as well as to evaluate the efficacy of Mg to facilitate the local anesthetic effect of Bupivacaine during peripheral nerve block.
*Methods:* Sixty patients, ASA physical status I, II & III, undergoing laser photocoagulation were randomly divided into 2 equal groups. Both groups received femoral nerve block using nerve stimulator. Patients of group A were given Bupivacaine and Magnesium sulfate, while patients of group B were given Bupivacaine and saline. Pain was assessed using Visual analogue scale (VAS). The duration of action of Bupivacaine was determined by assessing the duration of sensory block, as well as, assessing the motor block of the quadriceps muscle in both groups. 75 mg of Diclofenac sodium was administered IM as a rescue analgesic. The total dose of the Diclofenac sodium used was recorded.
*Results:* The current study showed a significantly shorter duration of action of Bupivacaine, with a significantly lower pain scores among patients of group A. On the other hand, bearable pain period was significantly shorter, and the total consumption of Diclofenac sodium in the 24 h postoperatively was significantly higher in group B.
*Conclusion:* The current study concluded that the admixture of magnesium to bupivacaine provides a profound prolongation of the femoral nerve block, in addition to a significant decrease in

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postoperative pain scores and total dose of rescue analgesia, with a longer bearable pain periods in the first postoperative day.



## 1. Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most abundant intracellular cation, it activates many of the enzyme systems involved in energy metabolism and acts as a natural calcium antagonist that regulates calcium access into the cell, in addition, Magnesium can be considered as a physiological blocker of N-methyl-D-aspartate (NMDA) receptors [1].

Magnesium (Mg) has antinociceptive effects due to its antagonistic effect of NMDA receptors [2]. N-methyl-D-aspartate (NMDA) receptors play a major role in central nociceptive transmission, modulation and sensitization of acute pain states [3]. In addition to their central location, recent studies identified NMDA receptors peripherally in the skin [4], muscles [5] and knee joints, and found that they play a role in sensory transmission of noxious signals [6]. In its inactive state, the NMDA receptor is blocked by the presence of a centrally positioned magnesium ion, the afferent activity in nociceptor fibers dislodges the central magnesium ion from the NMDA receptor, therefore allowing calcium influx into the cells [7].

The nerve stimulation is a well established method of nerve location during applying a peripheral nerve block, generally, it is accepted that the generated electrical current at the tip of the insulated needle used in the block produces a motor response before the needle enters the perineurium or even comes in direct contact with the nerve, so reducing the incidence of nerve trauma and intraneural injection [8,9]. We hypothesized that the addition of Magnesium sulfate to local anesthetics during peripheral nerve block would prolong the duration of the block.

The aim of this randomized, double-blinded, placebo-controlled study was to investigate the potential analgesic effect of Magnesium sulfate and its possible efficacy to prolong the duration of action of Bupivacaine when administered together for the femoral nerve block in patients undergoing laser photocoagulation of varicose veins of lower limbs.

## 2. Patients and methods

After obtaining approval from the Clinical Research Ethics Committee of Erfan and Bagedo General hospital and obtaining informed consent, Sixty patients, ASA physical status I, II & III, undergoing laser photocoagulation for varicose veins of the lower limb were included in this study. The patients were randomly divided into 2 equal groups: Group A patients ($n$ = 30) received femoral nerve block with Bupivacaine and Mg and Group B patients ($n$ = 30) received femoral nerve block with Bupivacaine and saline. Inclusion criteria were as follows: age > 18 yr old; ability to consent; and ability to understand and communicate, Exclusion criteria were cardiovascular, hepatic or renal dysfunction, neuromuscular diseases, opioid or analgesic abuse, and prior treatment with calcium channel blockers.

All patients were premedicated with 5 mg midazolam I.M. 30 min before shifting to OR. After admission to OR, the standard monitors including noninvasive arterial blood pressure, electrocardiography and pulse oximetry were applied. A 20 gauge intravenous catheter was inserted. With the patient in supine position and an oxygen open facemask applied at 5 L/min, the inguinal region was exposed and scrubbed with povidone iodine solution. The site of the needle insertion was identified as a point 1 cm lateral to the femoral artery at the level of the inguinal crease, and this site was anesthetized with 2 ml lidocaine 2%. A 21 gauge, 50-mm insulated stimulating needle (Simplex A-B Braun Melsungen AG 34209 Melsungen Germany) was used; it was connected to the nerve stimulator (Pajunk nerve stimulator multistim sensor. Karl-Hall-Strabe 1-D-78187 Geisingen Germany), with the nerve stimulator being connected to an ECG electrode applied on the lateral side of the thigh of the patient. The nerve stimulator was set at 1.5 mA, 2 Hz, 0.1 ms, and the needle was inserted through the skin and propagated gradually in a cephalad direction at a 45° angle to the skin surface while maintaining needle orientation in a parasagittal plane till the femoral nerve was stimulated resulting in contraction of the Quadriceps Femoris which cause proximal patellar movement. The needle was positioned to optimize the muscle contraction, and then the current was decreased gradually until the best muscle contraction was obtained at a current of 0.2–0.4 mA.

In group A, patients were injected with 20 ml Bupivacaine 0.25% and 5 ml of magnesium sulfate 10% solution (500 mg) a total volume of 25 ml, through the needle directly on the femoral nerve, While in group B, patients were injected with 20 ml Bupivacaine 0.25% and 5 ml normal saline 0.9%, a total volume of 25 ml. All the patients enrolled in the study were randomly assigned using concealed envelope method to one of the two groups, in addition, patients as well as the anesthetist and the surgeon were blinded to the type of the medications injected and the master codes were kept with a person that does not share in the collection or analysis of the results.

The severity of pain was assessed using 10 mm linear Visual analogue scale (VAS), where a score of 0 was considered as pain free, while a score of 10 was considered as the worst imaginable pain. Pain was assessed at 1, 3, 6, 12, and 24 h postoperatively. Furthermore, the duration of action of Bupivacaine was determined by assessing the sensory block at the antromedial aspect of the middle third of the thigh using pinprick method compared with the same site in the contralateral thigh as a reference, as well as, assessing the motor block of the quadriceps muscle, both of which were recorded every 30 min. The duration of sensory block was considered as the time interval between the local anesthetic injection and the complete recovery of sensation, and the duration of motor block was the time interval from local anesthetic injection till the recovery of motor activity.

If the VAS pain scores recorded increases more than 5, Diclofenac sodium 75 mg was administered IM as a rescue analgesic. The total dose of the Diclofenac sodium used was recorded. Bearable pain period was measured and is defined as the time from injection of the local anesthetic and the studied drug (Mg) during block placement till the first injection of the rescue analgesia. Side effects of Mg such as flushing, sedation, and decrease in mean blood pressure, or heart rate by more than 15% of the initial baseline value were recorded at the same time interval as done for the VAS.

Data were analyzed using computer statistical software system SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Patient characteristic data, operative time and time delay between block placement and supplementary analgesic administration were analyzed using two-tailed unpaired *t*-tests. Differences between the groups in pain scores and total diclofenac consumption were analyzed using Mann–Whitney U-test. The number of patients requiring diclofenac was compared between groups using $x^2$-test with Yates correction. Descriptive data are expressed as mean (±SD). Sample size was estimated using pain scores as the primary variable. Assuming a SD of 1 cm, we calculated a group size of 30 patients which would be sufficient to detect a difference of 1 cm on the VAS at an alpha threshold of 0.007 with 90% power. A *P*-value lower than 0.05 was considered statistically significant.

## 3. Results

The current study showed no significant differences in demographic data including sex, age, body weight or height between group A and group B as shown in (Table 1). The mean duration of the surgical Laser Photocoagulation procedure was close to each other in both groups, with no statistically significant difference (Table 1).

The duration of action of Bupivacaine as determined by both the motor block and the sensory block which were assessed every 30 min, was found to be significantly longer in group A i.e. with the addition of Mg than in group B as shown in (Fig. 1).

As regards the severity of pain as assessed by VAS, the results were as follows; in group A at 1 h postoperatively (1.5 ± 0.61), at 3 h (2.5 ± 0.49), at 6 h (2.9 ± 0.91), at 12 h (3.2 ± 1.30), and finally at 24 h (1.1 ± 0.21), on the other hand, in group B, at 1 h (7.8 ± 1.29), at 3 h (6.1 ± 1.01), at 6 h (5.9 ± 1.02), at 12 h (4.8 ± 0.12), and at 24 h (4.2 ± 1.76), indicating a significantly lower pain scores among patients of group A as expressed in Fig. 2.

Bearable pain period was significantly shorter in group B (55 ± 11 min) when compared with that of group A (672 ± 189 min) and this is expressed in Fig. 3, furthermore, the total consumption of Diclofenac sodium in the 24 h postoperatively was significantly higher in group B (113.6 ± 43.87 mg) than in group A (35.6 ± 39.15 mg) as shown in Table 2.

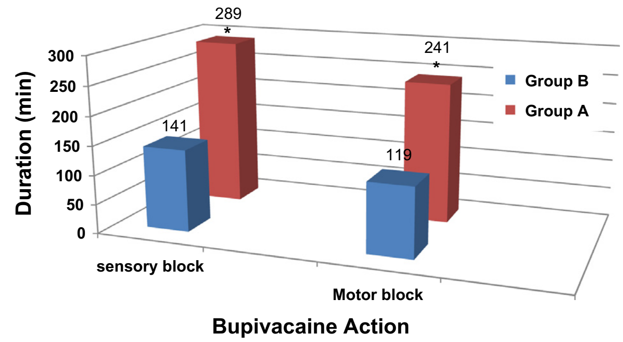


**Figure 1** The duration of action of Bupivacaine. *Significant difference.

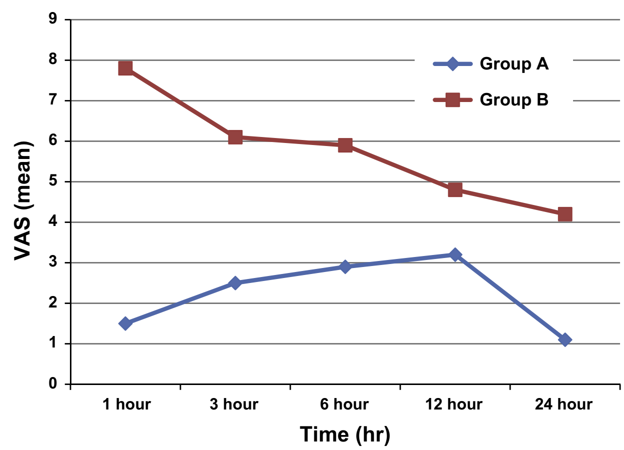


**Figure 2** Pain scores as assessed by Visual analogue scale at 1, 3, 6, 12, and 24 h postoperatively for patients of both groups. *Significant difference.

## 4. Discussion

In the present study, we found that the use of Magnesium sulfate as an additive to the local anesthetic Bupivacaine during peripheral nerve block improve postoperative pain score in patients undergoing laser photocoagulation surgery, with a longer duration of time till the need for a rescue analgesia and a lower total dose of analgesics used, in addition, it prolongs the duration of action of Bupivacaine.

Aiming for improvement and facilitation of fast rehabilitation and recovery after surgery, our study was directed towards better postoperative analgesia. Numerous clinical investigations have demonstrated that Mg infusion during

**Table 1** Demographic and operative data. Values are expressed as mean ± SD.

| | Group A ($n$ = 30) | Group B ($n$ = 30) |
|---|---|---|
| Age (year) | 31.6 ± 1.3 | 32.4 ± 1.9 |
| Gender (M/F) | 9/21 | 6/24 |
| Body weight (kg) | 60 ± 30 | 56 ± 28 |
| Height (cm) | 159 ± 3 | 154 ± 5 |
| Duration of surgery (min) | 69 ± 25 | 73 ± 29 |

No significant differences between the two groups.

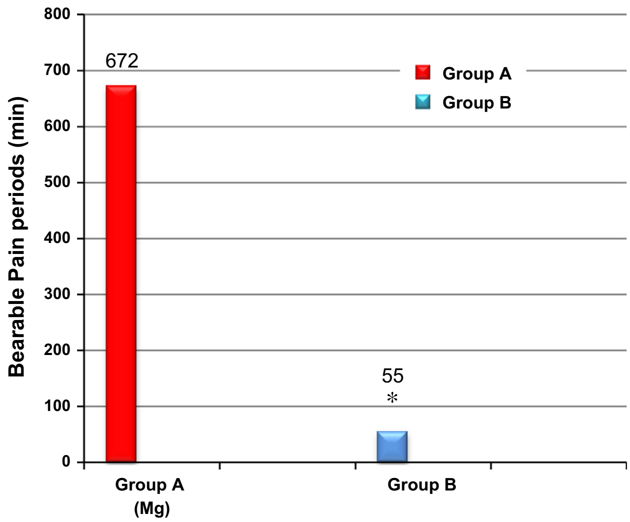


**Figure 3** The bearable pain periods of both groups. *Significant difference.

general anesthesia reduces anesthetic requirement and postoperative analgesic consumption; in addition, its administration also leads to a significant reduction in analgesic consumption during the intra-operative period [10–12]. The intrathecal as well as the systemic administration of Magnesium sulfate improves postoperative analgesia due to its antagonistic effect on NMDA receptors [10,13,14], Moreover, postoperative analgesic effect of Magnesium has been studied by many authors, most of which showed in their studies that the systemic use of Magnesium minimizes the postoperative analgesic requirement and discomfort [15,16], so we were interested to determine whether Magnesium can provide similar analgesia if injected directly on the peripheral nerves during peripheral nerve block. It is suggested that magnesium affects peripheral nerves as it interferes with releasing neurotransmitters at the synaptic cleft or potentiates local anesthetics action [17], besides, a potential interaction between local anesthetics and high magnesium concentration in frog sciatic nerve block was suggested by Akutogawa et al. [18].

Supporting the results of the present study was the results of Mizutani et al. [19], done on healthy adult volunteers to study the analgesic effect of iontophoresis with Magnesium, which showed a significant prolongation of block duration thus supporting the view that Magnesium has a good analgesic effect resulting in a better pain relief clinically. Furthermore, Aytac et al. [20], studied the duration of axillary plexus block when Magnesium sulfate is added to Prilocaine, and concluded that the use of magnesium with prilocaine during the block causes a profound prolongation of both the motor and sensory effect of prilocaine without side effects, suggesting that magnesium may be a useful adjuvant to local anesthetics. This goes with the reported data that magnesium produces a state of general anesthesia and promotes the activity of local anesthetic agents [21]. Moreover, Elsharnouby et al. [22] reported a significant reduction in the total dose analgesia during their study of the use of magnesium sulfate in hypotensive anesthesia. Also, Hwang et al. [2], studied the use of magnesium during spinal anesthesia to improve postoperative analgesia and reported a significant lowering in the VAS in patients receiving magnesium during total knee replacement, but unlike the present study no significant differences were detected as regards the need for postoperative rescue analgesia. On the contrary to our study, Hung et al. [23] studied the effect of magnesium sulfate on amide local anesthetics in rat sciatic nerve block and concluded that magnesium shortens the duration of sciatic nerve block with amide local anesthetics thus does not seem to be useful adjuvant to local anesthetics in peripheral nerve block. However, Bondok et al. [24] studied the effect of intra-articular magnesium in knee arthroscopy, and showed that magnesium resulted in a significant decrease in the postoperative VAS in the first 24 h which become less significant thereafter, in addition to, significant decrease in the dose of postoperative rescue analgesia with a longer delay in the need for that analgesia, concluding that intra-articular magnesium can be a useful alternative for postoperative analgesia. Furthermore, Kashefi et al. [25] studied the effect of adding magnesium to lidocaine during intravenous regional anesthesia, and found out that magnesium sulfate enhances the quality of anesthesia and analgesia during regional intravenous anesthesia without causing side effects.

In conclusion, the results of this clinical study showed that the admixture of magnesium sulfate to local anesthetic bupivacaine during femoral nerve block provides a profound prolongation of the duration of both sensory and motor block, in addition to a significant decrease in postoperative pain scores and total dose of rescue analgesia, with a longer bearable pain periods in the first postoperative day. Further studies are required to evaluate other doses, toxicity, and other groups of local anesthetics, in addition to comparing the effect of single perineural injection and perineural infusion of magnesium on postoperative pain. Moreover, the assessment of the results for a longer duration than the first postoperative day as well as in major surgical procedures may be beneficial.

## Conflict of interest

We have no conflict of interest to declare.

**Table 2** Total consumption of Diclofenac Sodium in the first 24 h postoperatively with the number of patients in both groups requiring rescue analgesia. Values are expressed as mean ± SD.

| | Group A ($n$ = 30) | Group B ($n$ = 30) |
|---|---|---|
| Diclofenac sodium (mg) | 35.6 ± 3915* | 113.6 ± 43.87 |
| Number of patients who needed rescue analgesia | 9/30* | 30/30 |

* Indicates significant differences between the two groups.

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