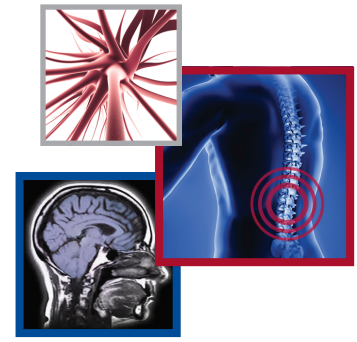
RESEARCH ARTICLE

Pain Management



Effect of magnesium sulfate on morphine activity retention to control pain after herniorrhaphy

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Summary points

- Our research was carried out to compare magnesium sulfate ($MgSO_4$) with isotonic saline in terms of pain control co-administered with morphine after herniorrhaphy.
- Our sample size was 100 patients who were candidates of herniorrhaphy randomized into two groups: experimental and control (50 patients in each).
- Spinal anesthesia was induced using 20% of 4 cc of morphine.
- The experimental and control group were administered after postoperation with 20% of 2 cc $MgSO_4$ in 2 cc of isotonic saline and 4 cc of isotonic saline, respectively.
- Our findings showed that $MgSO_4$ increased the potency of morphine thereby reducing the amount of postoperative pain killer needed.
- This approach to the therapy of surgical pain is a potential mechanism for successful analgesia formulation.

Aim: This research was carried out to compare magnesium sulfate ($MgSO_4$) with isotonic saline in terms of pain control after herniorrhaphy. **Patients & methods:** A randomized double-blind study, in which the patients were blind to all. A total of 100 patients who were candidates of herniorrhaphy were randomized into two groups: experimental and control (50 patients in each). Anesthesia was induced with 20% of 4 cc of morphine. The experimental and control group received postoperative 20% of 2 cc $MgSO_4$ in 2 cc of isotonic saline and 4 cc of isotonic saline, respectively. **Result:** The administration of postoperative morphine in control group 0.79 ± 1.48 mg was significantly higher to the experimental group 0.17 ± 0.63 mg during the first 24 h ($p = 0.01$). **Conclusion:** $MgSO_4$ increased the potency of morphine thereby reducing the amount of postoperative pain killer needed.

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KEYWORDS
• herniorrhaphy
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• morphine • pain

Magnesium (mg) is the fourth most abundant cation in the body, and the second most abundant intracellular action after potassium [1,2]. Approximately one half of the total body mg is present in bones and 20% in skeletal muscles [3]. Magnesium is necessary for the presynaptic release of acetylcholine from nerve ending and may produce an effect similar to calcium entry blocking drugs [4]. Magnesium and the NMDA receptor are thought to be involved in the modulation of pain [5,6]. This metal with a valency of 2+ has been said to inhibit calcium entry into the cell via a noncompetitive NMDA receptor block, it is a physiological calcium antagonist at different voltage-gated

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channels. Magnesium blocks NMDA channels via voltage-dependent mechanism and creates a cutback of NMDA-induced currents. These channels may be important in the antinociception mechanism [7]. Effective postoperative analgesia may facilitate recovery and reduce morbidity in surgical patients [8,9].

Noxious stimulation leads to the discharge of aspartate and glutamate neurotransmitters, which is coupled to the NMDA receptor [10]. Activation of these receptors produces calcium entry into the cell and series of central sensitization, such as long-term potentiation and wind-up in spinal cord, is generated in response to cells prolong stimuli [11,12]. NMDA receptor signaling may be crucial in regulating the period of acute pain [13]. Magnesium blocks calcium influx and antagonizes NMDA receptor channels noncompetitively [14].

Magnesium sulfate ($MgSO_4$) has been previously investigated as a possible adjuvant for intra and postoperative analgesia. In previous studies, it was shown that intrathecally administered mg increases the duration of action of spinal opioid analgesia both in human and rats [15,16]. Spinal anesthesia of mg promotes postoperative analgesia after orthopedic surgery [17]. $MgSO_4$ intrathecal addition to the combination of 10 mg bupivacaine and 25 µg fentanyl prolonged spinal anesthesia in patients with lower extremity surgery [18–20]. The mechanism behind this is the modulation of Ca influx into the cell. Magnesium has also been said to prevent central sensitization from peripheral nociceptive stimulation [21,22].

In this regard, our study aims to evaluate the effect of $MgSO_4$ on postoperative morphine usage reduction for pain control after herniorrhaphy.

Patients & methods

This is a double-blind randomized study, in which the patients were blind to all. In this clinical trial, a total of 100 patients who were candidates for herniorrhaphy, were randomly divided into experimental (50 cases) and control (50 cases) groups. This double-blind randomized study compares $MgSO_4$ with isotonic saline in terms of pain control after herniorrhaphy. An independent ethical committee approved the protocol design. Several investigators were recruited. Written informed consent was obtained from patients aged 18–70 years **(Table 1)**.

Inclusion criteria includes patients who scheduled for initial open inguinal hernia repair with Shouldice or apparented procedures under spinal anesthesia. The randomization was done centrally as blocks of four and with a 2:2 treatment ratio. Allocation was carried out on the basis of one complete treatment block.

To keep the double-blind assignment, the treatments were made by a third person chosen by the investigators. This third person did not have any contact with the patient or the investigator over the whole trial.

• Intervention

In the experimental group, 20% of 2 cc $MgSO_4$ in 2 cc of isotonic saline was administered to the patient by local injection in a double-edged surgical incision immediately after surgery. In the control group, only 4 cc isotonic saline was administered to the patient after surgery. Patients received spinal anesthesia induced by 20% of 4 cc morphine using a standard midline approach in the sitting position.

• Herniorrhaphy technique

The mesh plug repair was employed in this study, which consists of a 2-inch groin incision. The external oblique muscle is cut opened toward its fibers. Without opening the sac, the cord is cut opened and the indirect sac is pushed back into the abdominal cavity. The peritoneal sac is not joined. Then, a plug is inserted in the deep ring and guided to the ring with prolene 2/0 interrupted stitches in three to four places. We excised a lipoma of the cord, when present. In the cases of direct hernia, the defect base is circumcised using electric cautery. The plug is then

Table 1. Demographic data.

Parameters	Experimental group	Control group	p-value
n	47	47	
Age (years)	45 (17–68)	39 (18–70)	
Height (cm)	176 (165–188)	179 (168–192)	p = 0.02
Weight (kg)	73 (65–81)	78 (70–86)	
Duration of surgery (min)	35 (30–50)	37 (30–55)	

Table 2. Comparison of mean (±standard deviation) heart rate between the two studied groups at different time intervals.

Time intervals	Experimental group	Control group	Significance
First 4 h	78.04 (±3.4)	78.96 (±5.2)	0.231
Second 4 h	78.76 (±3.9)	79.78 (±4.9)	0.177
Third 4 h	79.12 (±2.7)	80.26 (±4.3)	0.143
Fourth 4 h	78.98 (±2.7)	78.66 (±4.7)	0.758
Fifth 4 h	79.16 (±2.3)	79.04 (±4.5)	0.763
Sixth 4 h	79.76 (±2.3)	79.40 (±2.9)	0.514
Overall	79.35 (±3.05)	79.35 (±4.46)	>0.05

placed and guided with three to four interrupted prolene stitches. An onlay mesh is inserted without securing it, but one prolene stitch is used for its lateral split end approximation. The external oblique is then closed with polysorb 2/0 and the skin is also dosed with subcuticular polysorb 3/0. For recurrent hernia repair, the sac is freed and decreased via the margins of the defect and a plug is placed into it to occlude the defect. The plug is finally secured with three to four interrupted prolene stitches. Median follow-up was 1 year (9–15 months).

• Efficacy assessments

Heart rate, systolic and diastolic blood pressures were measured and recorded. For measurement of the pain severity, a visual analog scale (VAS) was used and the amount of morphine used in six 4-h intervals in the first 24 h after surgery was recorded as well. Surgical intervention was performed by several surgeons (five in total). Injections were performed locally at the site of incision in a double-edged surgical incision. The operative duration was similar in nearly all patients. Informed consent was taken from all the participants. Second group of the patients were injected based on priorities for the remaining syringes block needles. Assessment of pain medication injected was done by someone else, who was unaware of the medications administered, pain scores were assessed in all patients by several researchers based on the VAS, and recorded. Descriptive indices such as mean ± standard deviation (SD) were used to express data statistically.

Results

Six patients were excluded from the study, two due to the administration of supplementary analgesics other than those prescribed from this study protocol, three due to missing data and one due to a failure in the inclusion procedure. Of the remaining 94 patients, the experimental and control group (n = 47 each) were administered with 20% of 2 cc $MgSO_4$ in 2 cc of isotonic saline and 4 cc isotonic saline, respectively. Demographic data, duration of surgery and preoperative consumption of morphine are shown in Table 1. Except for body height, no significant differences were observed between the groups.

Average (±SD) heart rate in the first 4-h postoperation in the experimental and control groups was 78.04 ± 3.4 and 78.96 ± 5.2; p = 0.231, respectively. Table 2 shows the heart rates at six intervals compared between the two groups as well as overall heart rate. There were no significant differences observed regarding this variable between the two studied groups.

Table 3 presented the average systolic blood pressures in the two groups, during the first 4-h postoperation, which were 115.5 ± 12.17 and

Table 3. Comparison of mean (±standard deviation) systolic blood pressure between the two studied groups at different time intervals.

Time intervals	Experimental group (mmHg)	Control group (mmHg)	Significance
First 4 h	115.5 (±12.17)	111.3 (±14.56)	0.941
Second 4 h	110.4 (±13.25)	112.8 (±19.52)	0.115
Third 4 h	113.9 (±18.02)	112.8 (±11.83)	0.738
Fourth 4 h	111.5 (±18.07)	110.8 (±14.82)	0.189
Fifth 4 h	112.1 (±12.25)	113.8 (±14.48)	0.861
Sixth 4 h	114.1 (±17.69)	117 (±13.3)	0.8907
Overall	112.65 (±14.21)	114.16 (±15.79)	>0.05

Table 4. Comparison of mean (±standard deviation) diastolic blood pressure between the two studied groups at different time intervals.

Time intervals	Experimental group (mmHg)	Control group (mmHg)	Significance
First 4 h	69.2 (±9.7)	70.7 (±11.42)	0.432
Second 4 h	70.4 (±10.04)	71.3 (±11.19)	0.793
Third 4 h	72.7 (±8.8)	70.7 (±10.4)	0.435
Fourth 4 h	70.8 (±8.9)	68.8 (±10.12)	0.227
Fifth 4 h	71.2 (±10.23)	70.97 (±10.77)	0.831
Sixth 4 h	72.5 (±8.1)	73.2 (±8.3)	0.632
Overall	71.13 (±9.9)	70.93 (±10.37)	>0.05

111.3 ± 14.56 mmHg in the experimental and control groups, respectively (p = 0.941). As it has been shown in the table, there was no significant differences were observed in terms of systolic blood pressure during the study period.

Table 4 presented the average (±SD) diastolic blood pressure in the first 4-h interval, it was 69.2 (±9.7) and 70.7 (±11.42) in the experimental and control group, respectively; p = 0.432.

In Table 5, the average VAS scores in the experimental and control groups in the first 4-h interval were 1.44 ± 1.9 and 2.98 ± 2.7 (p = 0.02), respectively. There is a significant difference in the VAS score at all time intervals between the two groups with regard to pain severity.

Table 6 shows the average dosages of morphine administered in the two groups, during the first 4-h postoperation time, the experimental and control groups dosage were 0.34 ± 1.1 mg and 0.96 ± 1.9 mg, respectively (p = 0.05). In general, median total morphine requirements in control group 0.79 ± 1.48 mg was significantly higher compared with the experimental group 0.17 ± 0.63 mg (p = 0.01). No wound infections or hematoma were observed postoperatively in any of the study groups.

In terms of pain relief within 24 h in $MgSO_4$ group, it seems that most of the discussion about preemptive analgesia can be maneuvered in the field.

Discussion

The results of our study showed that, there were no significant differences between the two studied groups regarding heart rate and systolic/diastolic blood pressures, 24-h after herniorrhaphy [23]. However, regarding the VAS score for pain severity and the dosages of morphine administered, significant differences were found [24,25]. The experimental group which received $MgSO_4$ showed better results in terms of pain control as compared with the control group which received only normal saline [26,27], this result is supported by Haidari *et al.* [17] and Fawcett *et al.* [28]. Our result is similar to the study of Ozalevli *et al.* [29], where mg group was found to delay sensory and motor block response, observing an identical delay in onset of spinal anesthesia when adding intrathecal mg to fentanyl and isobaric bupivacaine. They proposed that the difference in pH and baricity of the solution having mg add to the delayed onset. Arcioni *et al.* [30], observed that there was a prolonged duration of motor and sensory block likewise the period taken for postoperative analgesia, but this was less than the mg group D. Arcioni *et al.*, also examined that epidural and intrathecal mg prolonged and potentiated motor and sensory block [31]. Our results are also similar with previous study conducted by Buvanendran *et al.* [32], conducted on patients who went through lower extremity

Table 5. Comparison of mean (±standard deviation) visual analog scale scores between the two studied groups at different time intervals.

Time intervals	Experimental group	Control group	Significance
First 4 h	1.44 (±1.9)	2.98 (±2.7)	0.02
Second 4 h	1.3 (±2)	3.72 (±2.9)	0.001
Third 4 h	1.16 (±1.4)	3.66 (±2.4)	<0.001
Fourth 4 h	1.02 (±1.7)	2.78 (±2.8)	<0.001
Fifth 4 h	0.48 (±0.9)	1.8 (±2.1)	0.001
Sixth 4 h	0.18 (±0.3)	0.68 (±0.9)	0.04
Overall	0.93 (±1.39)	2.6 (±2.33)	0.01

Table 6. Comparison of mean (±standard deviation) doses of morphine administered between the two studied groups at different time intervals.

Time intervals	Experimental group (mg)	Control group (mg)	Significance
First 4 h	0.34 (±1.1)	0.96 (±1.9)	0.05
Second 4 h	0.22 (±0.7)	1.94 (±2.5)	0.001
Third 4 h	0.2 (±0.9)	1.02 (±1.18)	0.02
Fourth 4 h	0.26 (±1)	0.66 (±1.5)	0.223
Fifth 4 h	0	0.2 (±0.9)	0.15
Sixth 4 h	0	0	–
Overall	0.17 (±0.63)	0.79 (±1.48)	<0.01

surgery during the anesthesia of the spine, addition of 50 mg of intrathecal mg to the combination of 15 mg bupivacaine and 5 µg fentanyl lengthened the duration of spinal anesthesia activity. After the addition of morphine to mg in the study group for herniorrhaphy anesthesia [33], the metal increases the pain relief duration as compared with the control group without the active ingredient [34]. These results were similar to anesthetic studies on animals, where intrathecal mg increased the analgesic duration of opioids [35–37].

Amr *et al.* [38] evaluated the analgesic and adverse effects of intrathecal dexmedetomidine when combined with $MgSO_4$ as an adjuvant in patients undergoing lower limb and lower abdominal surgery via bupivacaine induced spinal anesthesia [39,40]. They found that adding 5 µg intrathecal dexmedetomidine to 50 mg intrathecal $MgSO_4$ ameliorated the quality of bupivacaine spinal anesthesia [6,41], and also improved postoperative analgesia in lower abdominal surgery [42,43]. There were no significant adverse effects in each of the groups. A decrease in the sedation score observed in mg group D is in support with a previous study that used 10 µg intrathecal dexmedetomidine in transuretheral resection of prostate patients [44,45]. The cause of sedation following intrathecal dexmedetomidine may be due to its systemic absorption and vascular redistribution to higher centers or cephalic migration in cerebrospinal fluid [46,47] (which is not observed in our study), although delayed onset of sedation is possible, it has not been reported [48,49].

The lack of sedative effect reported by Strebel *et al.* [50], with doses of clonidine as high as 150 µg is likely due to its receptors lower affinity. Sedation from epidural clonidine represents an α-2-adrenergic effect and it has been reversed by yohimbine; a relatively specific α-2-antagonist in postoperative patients.

Conclusion

According to our results, there were no significant differences between the two groups studied regarding heart rate and systolic/diastolic blood pressures in the first 24 h after herniorrhaphy. There was a significant difference found between the VAS score for pain severity and the dosages of morphine administered [51]. The experimental group which received $MgSO_4$ showed better results in terms of pain control extension as compared with the control group which received only isotonic saline. This approach to pain therapy is a potential mechanism for successful analgesia formulation. Further studies are needed to determine whether larger doses of morphine and $MgSO_4$ can produce greater potential for analgesia, and reduce opioid requirements or inhibition of the process.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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