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# Safety and efficacy of different doses of intrathecal magnesium sulfate on the acute and chronic postoperative pain in patient undergoing pelvic cancer surgeries - a randomized controlled dose finding clinical study

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**ABSTRACT**

**Background and objectives:** Excision of tumors from pelvis causing severe pain postoperatively. Hemodynamic stability, and better analgesia were documented when MgSO4 was used as an adjuvant to local anesthesia. We aimed to investigate the effect of using intrathecal MgSO4 with different doses as an adjuvant to LAs on postoperative acute pain, hemodynamics, and chronic pain.

**Methods:** Ninety patients scheduled for pelvic surgery for excision of tumors have been included in this study and divided into three groups; all patient received general anesthesia (GA) plus intrathecal fentanyl (group A), while the second (group B) and the third (group C) received intrathecal magnesium sulfate 50 mg and 100 mg, respectively; intra- and postoperative outcomes such as hemodynamics, (LANSS) pain score, (NRS) and postoperative complications have been measured.

**Results:** The results revealed that MgSO4 in the (group B) had significant effect on decreasing the postoperative pain during the first 24 hours; the result of the three groups revealed that there was statistically significant difference between the group A and groups (B-C) (P-value >0.05), while there was insignificant statistical difference between the group B and group C. Patients in the fentanyl group requested analgesic after 6 to 8 hours (mean ±SD 8.4817 ± 0.819 mg), while patients in group B after 12 to 14 hours postoperatively (13.7450 ± 0.86477 mg) and patients in group C requested analgesia 16 hours postoperatively (13.7800 ± 1.00272 mg). LANSS score was significantly improved in groups B-C, but fewer complications such as itching, nausea and shorter time of recovery after the surgery in group B than other groups.

**Conclusion:** When comparing IT magnesium sulfate at doses of 50 and 100 to fentanyl 50 mg, we found superiority of MgSO4, in decreasing pain after surgery and ITMgSO4 50 mg achieved a reasonable balance between postoperative analgesia and side effects. In addition, ITMgSO4 has shown significant effect in decreasing the chronic pain postoperatively.

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Magnesium sulfate; chronic pain; pelvic cancer surgeries; NRS; LANSS score

## 1. Introduction

Tumors that originate in the pelvis account for one-sixth of all sarcomas [1,2]. Due to the presence of nerves and blood vessels inside the pelvic cavity, organs and viscera, as well as muscles that originate from the pelvis' inner and exterior surfaces and go from the pelvic cavity to the rest of the body, the pelvis is a difficult location to operate on [3–5].

Abdominal wall soft tissue tumors can be of varying degrees of malignancy, from benign to extremely aggressive. The most prevalent types of soft tissue tumors are desmoid tumors (DT) and soft tissue sarcomas (STS) [6].

Surgical excision of tumors from abdomen and pelvis is considered one of the major surgeries that include severe pain postoperatively. Pain is a common side effect of most surgeries, but some surgeries may cause more pain than others [7].

It has been suggested that fentanyl, when combined with local anesthetics for spinal anesthesia, can increase the duration of postoperative analgesia [8].

More hemodynamic stability and fewer adverse effects were documented when magnesium sulfate ($MgSO_4$) was used as an adjuvant to bupivacaine, and it is noted that this combination can lengthen the duration of analgesia [9,10].

Intraoperatively and postoperatively, $MgSO_4$ can lessen the need for anesthetic agents and painkillers [11]. In addition, catecholamine secretion is suppressed, which is a problem during surgery [12]. Either a bolus dose of magnesium given intravenously

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[13] just before inducing general anesthesia or a continuous infusion of magnesium given during the anaesthetic can help reduce muscle tension and relax the patient [14].

This study aimed to investigate the effect of using intrathecal magnesium sulfate with different doses as an adjuvant to local anaesthetic agent on perioperative acute pain, hemodynamics and chronic pain.

## 2. Materials and methods

Informed consent was obtained from all patients participated in the study. This double-blind randomized prospective study included patients who underwent pelvic surgery for excision of tumors such as ovarian tumors, testicular tumors, uterus tumors, urethral tumors and prostate tumors. Patients who were older than 18 years old, diagnosed of pelvic cancer and had to undergo a surgery to excise it were participated in the study. Patients who refused to participate, patients on chronic analgesic use and patients who had renal or cardiac conditions or any contradicting condition with fentanyl or $MgSO_4$ were excluded from the study. Eligible patients was assigned to each group by a closed opaque envelope.

The randomization process was performed by an impartial biostatistician who was not involved in participant recruitment or clinical care. The treatment allocation sequences for each participant were generated using a computer-generated random number sequence. The type of anesthetic allocation was concealed by placing it in sealed opaque envelopes. The envelopes were numbered in sequential order and stored in a secure manner. After participants enrolled and completed baseline assessments, study personnel assigned the next available numbered envelope to each participant in sequence. Upon opening the envelope, the treatment group assigned to the participant was revealed. Both the trial participants and investigators were blinded to the treatment assignments. The use of opaque envelopes ensured the concealment of treatment allocation until the moment of envelope opening.

The actual study start date was on 1 January 2019 and completed on 8 September 2022. Institutional Review Board (IRB) approval was obtained from our institute, and 90 patients participated in the study after taking a written consent according to the ethical considerations. The authors registered the trial at Clinical Trials.gov with a unique ID number NCT03459417 at 12 November 2019 and conducted it according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

The performed study included 90 patients who were divided into three equal groups ($n = 30$). All patients in the three groups were anesthetized with standard GA plus subarachnoid block using 8 mg bupivacaine which was done before induction. In addition, intrathecal fentanyl 50 mic was added to subarachnoid block in the first group of patients. Group 2 received 50 mg $MgSO_4$ added to bupivacaine, whereas group 3 received 100 mg $MgSO_4$added to bupivacaine. The net volume of mixture injected in subarachnoid block was 3 ml. We compared the three groups in terms of intraoperative parameters and postoperative outcomes.

Intraoperative outcomes included systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and total consumption of inhaled anesthetic agent.

Postoperative outcomes including (MAP) and (HR) were measured every 4 hours after the surgery for 24 hours. Numerical rating scale (NRS) was used to assess the pain after surgery each 4 hours for the first 24 hours after the surgery. The time to first analgesic request and the total analgesic consumption during the first postoperative 24 hours were recorded. The degree of sedation measured by Ramsay sedation score and complications such as nausea, vomiting, respiratory depression, hypotension, headache, visual changes and bradycardia were assessed. The last outcome was the LANSS score to measure the chronic pain over 3 months postoperatively twice a month.

### 2.1. Collected data and statistical analysis

Demographic data including BMI, age, sex, type of operation and its duration and time of ambulation in addition to operation time were collected. Intraoperative and postoperative data were gathered through readings and assessments using scores and previously mentioned scales. The primary outcomes were considered to be NRS, total consumption of opioids during the first 24 hours postoperatively, chronic pain by LANSS score and complications including nausea, vomiting, itching and headache. The secondary outcomes included intra- and postoperative hemodynamics, total consumption of inhaled anesthetic agent and sedation score. Data were tabulated and analyzed using SPSS statistical package for social science (version 23). Mean, standard deviation and *P-value* were used to assess the statistical differences between groups. Confidence interval was used to compare between groups. Box plot was used to assess data spread.

## 3. Results

The total number of patients participated in the study ($n = 90$) is shown in Figure 1, with age range between 18 and 75 years old with mean (SD) ($44.2 \pm 4.5$), ($43.6 \pm 4.2$) and ($43.6 \pm 4.2$) for the three groups, respectively ($P = 0.072$). BMI ranged between 20 and 30 with mean (SD) ($25.5 \pm 2.3$) for fentanyl group (group A), ($25.4 \pm 2.6$) for $MgSO_4$ (50 mg) group (group B) and ($26.6 \pm 3.1$)

for $MgSO_4$ (100 mg) group (group C). No significant difference was found between the three groups ($P = 0.192$). Male patients distributed randomly between the three groups with percent 37%, 43%, 53% for the three groups, respectively. Also females distributed randomly with the following percentage between the three groups (63%, 57% and 47%), respectively, with no significant difference between the three groups ($P = 0.434$). The operation time ranged from 2.5 hours to 4 hours. There was no significant difference between the three groups ($P = 0.844$). All patients underwent pelvic and lower abdominal surgeries to remove either benign or malignant tumors. No significant differences were found between the three groups according to the type of operations ($P = 0.959$). Table 1 demonstrates the results.

Intraoperative parameters measurements included hemodynamic parameters (systolic (SBP) and diastolic blood pressure (DBP), heart rate in addition to measurements of total consumption of inhaled anesthetic agent (Sevoflurane). The results of the study revealed that there was a slight decrease in patients' hemodynamic parameters in (group A) as SBP/DBP mean was (106.83/70.17) mmHg and SD was (10.706/7.250) mmHg. In group B the mean of BP was (114.33/76.33) mmHg and SD was (10.063/6.687) mmHg, while in group C the mean of BP was (116/76.67) mmHg and SD (12.205/8.023). The results of the three groups revealed that there was no statistically significant difference between the three groups.

HR rate in group A was (66.63 ± 5.968) bpm, while group B (67.83 ± 5.826) bpm and in group C was (66.17 ± 6.909) bpm which indicated that there was no differences between the three groups in terms of the mean HR and mean BP.

Total consumption of inhaled anesthetic agent (Sevoflurane) varied insignificantly among the three groups where the mean and SD in group A was (7.85 ±

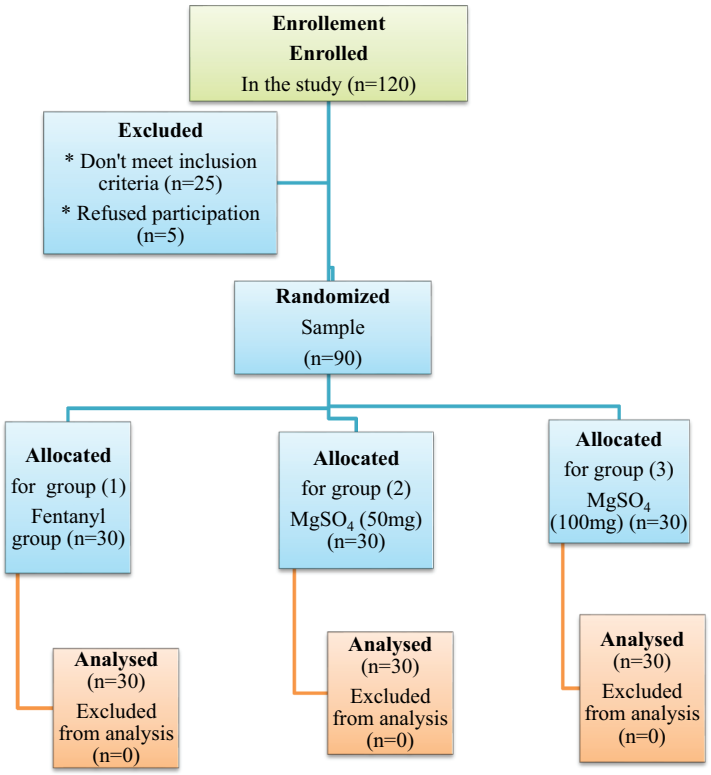


**Figure 1.** Flowchart diagram for study participants.

**Table 1.** Demographic data of the participants.

| | N | Mean | Standard deviation (SD) |
|---|---|---|---|
| Age | 90 | 48.015 | 17.017 |
| Gender | 90 | 1.48 | 0.502 |
| BMI | 90 | 24.85 | 2.44 |
| Operation time | 90 | 3.19 | 0.415 |
| Operation type | 10 | | |
| • Urethral tumors | 15 | | |
| • Uterus tumors | 16 | | |
| • Ovarian tumors | 12 | | |
| • Vaginal tumors | 20 | | |
| • Prostate tumors | 12 | | |
| • Testicular tumors | | | |

1.187) ml, while in group B mean and SD was (8.49 ± 1.183) ml, and in group C mean and SD was (9.19 ± 1.209) ml (Figure 2).

Patients in group A assessed their pain with higher scores on NRS ranged between (7 and 10), the mean and SD was (44.20 ± 5.275), while patients in group B assessed their pain with lower scores ranged between (5 and 7). The mean and SD of this group was (28.93 ± 3.991). Patients in group C assessed their pain with low scores ranged between (6 and 8) with mean and SD (28.13 ± 3.579). There was a statistically significant difference between group A, B and C groups, according to the results from the three groups (*P*-value <0.001), while there was insignificant statistical difference between the group B and group C where *P*-value <0.05 (Table 2, Figure 3).

Patients in group A requested analgesic for the first time postoperatively after 6 to 8 hours with mean ±SD (8.4817 ± 0.81995) hours, while patients in group B requested analgesic supplementation after 12 to 14 hours postoperatively with mean ±SD (13.7450 ± 0.86477) hours, while patients in group C requested analgesic agents 14 to 16 hours postoperatively with mean ±SD (13.7800 ± 1.00272) hours. Results revealed that there was statistically significant difference between group A and group B and group C (*P*-value <0.05), while there was an insignificant statistical difference between group B and group C (*P*-value >0.05) (Table 2, Figure 4).

Analgesic consumption was measured by the consumed amount of opioids given by PCA device during the first 24 hours postoperatively. In group A the mean±SD of analgesic consumption was (11.883 ± 1.3562) ml. In group B, the mean±SD of analgesic consumption was (5.333 ± 0.5774) ml, while in group C, it was (4.283 ± 0.6783) ml. Results demonstrated the significant differences in the total analgesic consumption between the group A and group B and between group A and group C, while there was insignificant statistical difference between groups B and C (Table 2, figure 5).

In group A, the mean±SD of sedation score was (4.70 ± 1.179), while in group B mean±SD was (1.63 ± 0.615) and in group C mean±SD was (2.03 ± 0.809). Results showed significant differences between group A and the two other groups, while it showed insignificant statistical differences between groups B and C (Table 2, Figure 6)

Chronic pain was assessed using LANSS score. Patients in group A showed delayed recovery rather than the patients in group B and C where the mean ±SD of group A was (71.57 ± 9.874). In group B; the mean ±SD was (30.43 ± 14.670), while the mean ±SD was (30.83 ± 17.128) in group C. Significant difference was noticed between the group A and group B and between group A and group C, while there was insignificant statistical difference between group B and group C (Table 2 and Figure 7).

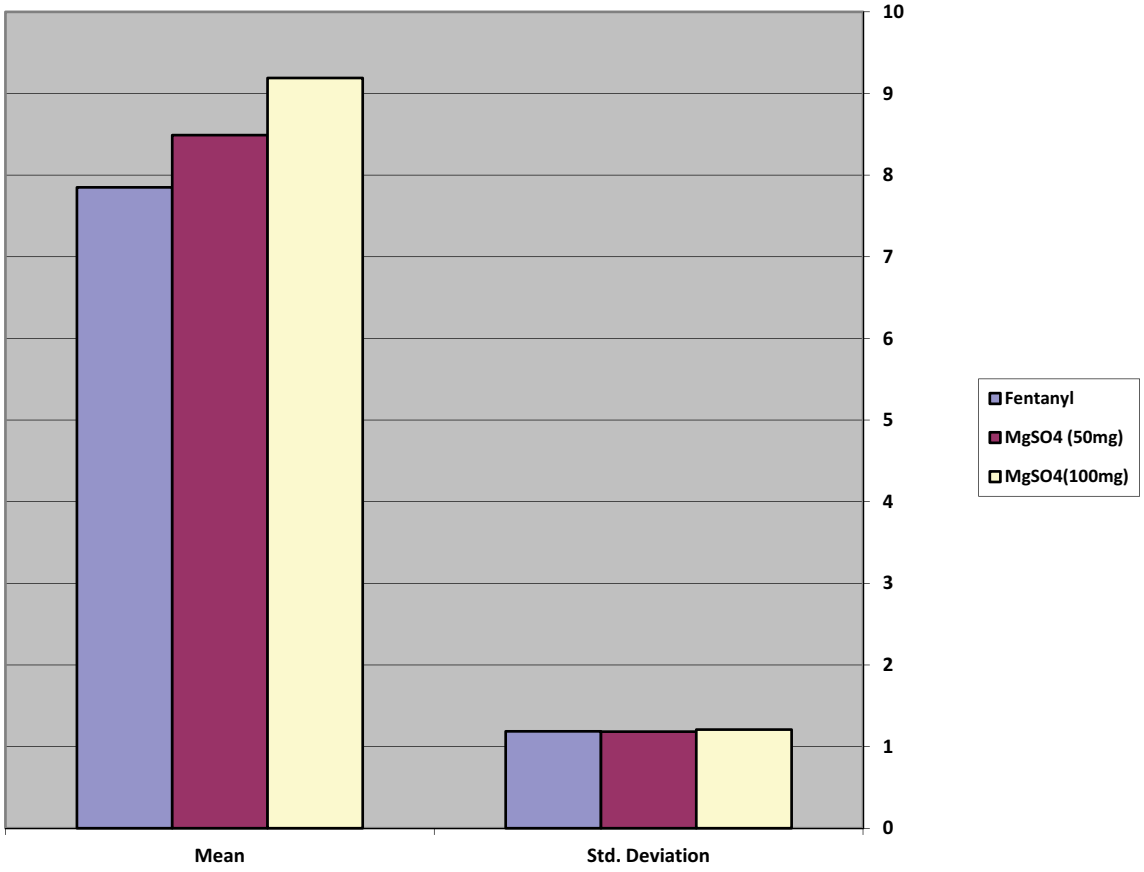


**Figure 2.** Mean and SD of the three groups according to total consumption of inhaled anesthetic agent.

**Table 2.** Differences between the three groups (NRS, first analgesic request, total opioids consumption, Ramsay sedation score, LANSS score and complications).

| Dependent Variable | (I) No. | (J) No. | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound | |
| NRS | Group A | Group2 | 15.27* | 1.12 | 0.000 | 12.47 | 18.06 |
| | | Group3 | 16.07* | 1.121 | 0.000 | 13.27 | 18.86 |
| | Group B | Group1 | −15.27* | 1.121 | 0.000 | −18.06 | −12.47 |
| | | Group3 | .80 | 1.121 | 0.776 | −1.99 | 3.59 |
| | Group C | Group1 | −16.07* | 1.121 | 0.000 | −18.86 | −13.27 |
| | | Group2 | −.80 | 1.121 | 0.776 | −3.59 | 1.99 |
| 1st analgesic request (12-15hrs) | Group A | Group2 | −5.26* | 0.23217 | 0.000 | −5.84 | −4.69 |
| | | Group3 | −5.3* | 0.23217 | 0.000 | −5.88 | −4.72 |
| | Group B | Group1 | 5.26* | 0.23217 | 0.000 | 4.69 | 5.84 |
| | | Group3 | −0.035 | 0.23217 | 0.989 | −0.61 | 0.54 |
| | Group C | Group1 | 5.3* | 0.23217 | 0.000 | 4.72 | 5.88 |
| | | Group2 | 0.035 | 0.23217 | 0.989 | −0.54 | 0.613 |
| Total opioids consumption | Group A | Group2 | 6.55* | 0.2419 | 0.000 | 5.95 | 7.15 |
| | | Group3 | 7.60* | 0.2419 | 0.000 | 6.99 | 8.20 |
| | Group B | Group1 | −6.55* | 0.2419 | 0.000 | −7.15 | −5.95 |
| | | Group3 | 1.05* | 0.2419 | 0.000 | 0.45 | 1.65 |
| | Group C | Group1 | −7.60* | 0.2419 | 0.000 | −8.20 | −6.99 |
| | | Group2 | −1.05* | 0.24 | 0.000 | −1.65 | −0.45 |
| Ramsay sedation score | Group A | Group2 | 3.07* | 0.22 | 0.000 | 2.49 | 3.64 |
| | | Group3 | 2.67* | 0.22 | 0.000 | 2.09 | 3.24 |
| | Group B | Group1 | −3.07* | 0.22 | 0.000 | −3.64 | −2.49 |
| | | Group3 | −0.40 | 0.22 | 0.232 | −0.98 | 0.18 |
| | Group C | Group1 | −2.67* | 0.22 | 0.000 | −3.24 | −2.09 |
| | | Group2 | 0.40 | 0.22 | 0.232 | −0.18 | 0.98 |
| LANSS score (neuropathic Pain) | Group A | Group2 | 41.13* | 3.60 | 0.000 | 31.99 | 50.27 |
| | | Group3 | 40.73* | 3.60 | 0.000 | 31.59 | 49.87 |
| | Group B | Group1 | −41.13* | 3.60 | 0.000 | −50.27 | −31.99 |
| | | Group3 | −0.40 | 3.60 | 0.994 | −9.54 | 8.74 |
| | Group C | Group1 | −40.73* | 3.60 | 0.000 | −49.87 | −31.59 |
| | | Group2 | 0.40 | 3.67 | 0.994 | −8.74 | 9.54 |
| Complications | Group A | Group2 | 3.23* | 0.249 | 0.000 | 2.61 | 3.85 |
| | | Group3 | 2.70* | 0.249 | 0.000 | 2.08 | 3.32 |
| | Group B | Group1 | −3.23* | 0.249 | 0.000 | −3.85 | −2.61 |
| | | Group3 | −.53 | 0.249 | 0.106 | −1.15 | 0.09 |
| | Group C | Group1 | −2.70* | 0.249 | 0.000 | −3.32 | −2.08 |

The complications such as nausea, vomiting and itching followed by the operations were common in the group C rather than in group B and group C. Statistical significant differences were noticed between group A and group B and between group A and group C. On the other hand, there was a statistically significant difference between group B and C (Table 2 and Figure 8).

## 4. Discussion

Pain that lasts more than three months or comes back after an initial resolution is considered chronic by the "International Association for the Study of Pain" (IASP) [15].

Primary and secondary chronic pain syndromes are distinguished in the new ICD category for chronic pain [16,17]. The term "chronic primary pain" describes a recently recognised medical disease in which pain persists despite the absence of any underlying structural or biochemical abnormalities. [18]. Six types of chronic secondary pain have been identified: chronic pain associated with cancer, chronic pain after surgery or trauma, chronic neuropathic pain, chronic pain in the head, face or jaw and chronic visceral pain [19,20].

Paul Janssen discovered and first synthesized fentanyl in 1960, revolutionizing the anaesthetic and pain-relieving potential of opioids. Fentanyl was the first fast-acting opioid found, and it was 50–100 times stronger than morphine and heroin (30–50 times) [21–25].

Patients who are about to have procedures done to their pelvis almost always get a bupivacaine subarachnoid block beforehand [22,26]. It is likely that the amount of bupivacaine administered intrathecally will not be sufficient to achieve complete anesthesia, because highly lipophilic short-acting opioids like fentanyl, when combined with local anesthetics, improve the quality as well as the length of anesthesia and analgesia in the obstetric population, which is why they are widely used to improve the quality of subarachnoid block [27–29].

Fentanyl, when administered intrathecally, exhibits a dose-related ceiling effect on respiratory depression, making it a preferred choice due to its reduced adverse effects such as nausea, vomiting and itching. This medication also induces desirable drowsiness during the postoperative period [30,31]. Despite its benefits, the optimal dosage for intrathecal fentanyl has not been definitively established. Studies evaluating

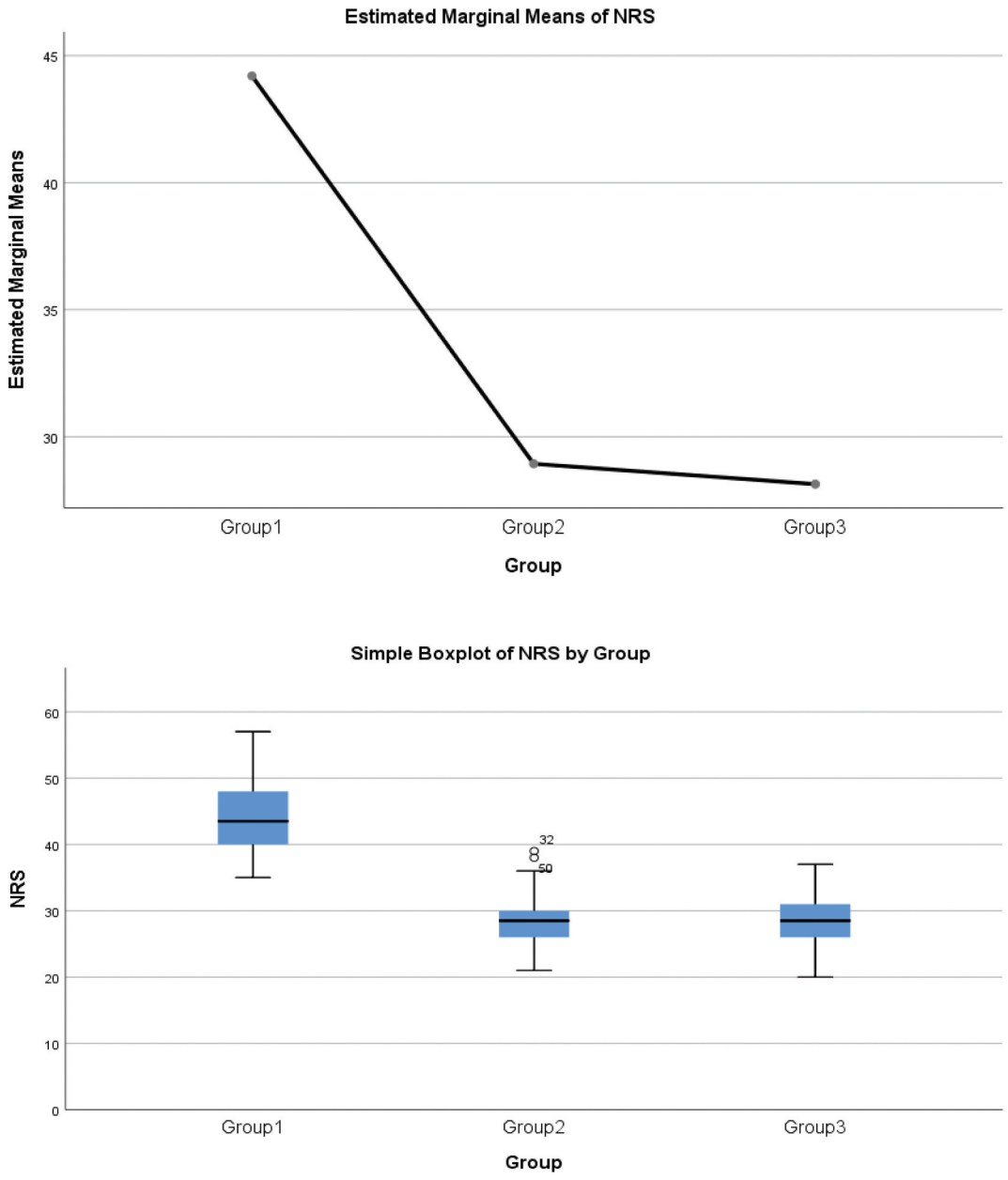


**Figure 3.** Box plot forNRS.

various dosages of intrathecal fentanyl did not find significant differences in secondary outcomes, such as pruritus, respiratory depression, nausea and vomiting. These findings were consistent across multiple investigations [32,33].

The previous findings are consistent with the results of our study which concluded that the use of fentanyl in the anesthesia of patients in the first group showed insignificant decrease in the mean heart rate and blood pressure.

$MgSO_4$ is widely used in anesthetic management [34]. It is known to preserve favorable hemodynamic [35], block acetylcholine releases at neuromuscular junctions [36] and potentiate the effects of non-depolarizing neuromuscular blockers [37].

Moreover, studies found that $MgSO_4$ reduces anesthetic requirements [38] shortens anesthetic induction [39] and diminishes total postoperative analgesic consumption [40] with no adverse complications [41,42].

The results of our study showed a significant delay in the timing of the first analgesic request during the first 24 hours in $MgSO_4$ groups, in contrast to what happened in the fentanyl group, and this is consistent with the study of Mostafa MF, et al [43], El Mourad MB, et al [44] who proved the delay of the first analgesic request.

Study of Hamdy Salman O, et al [45] and the study of Li LQ, et al [46] showed the superiority of magnesium sulfate over fentanyl in increasing the time until the first request for analgesic.

This is not the only advantage for using intrathecal magnesium sulfate as the results of our study also showed a significant decrease in the amount of analgesic consumed after operations, which is consistent with the

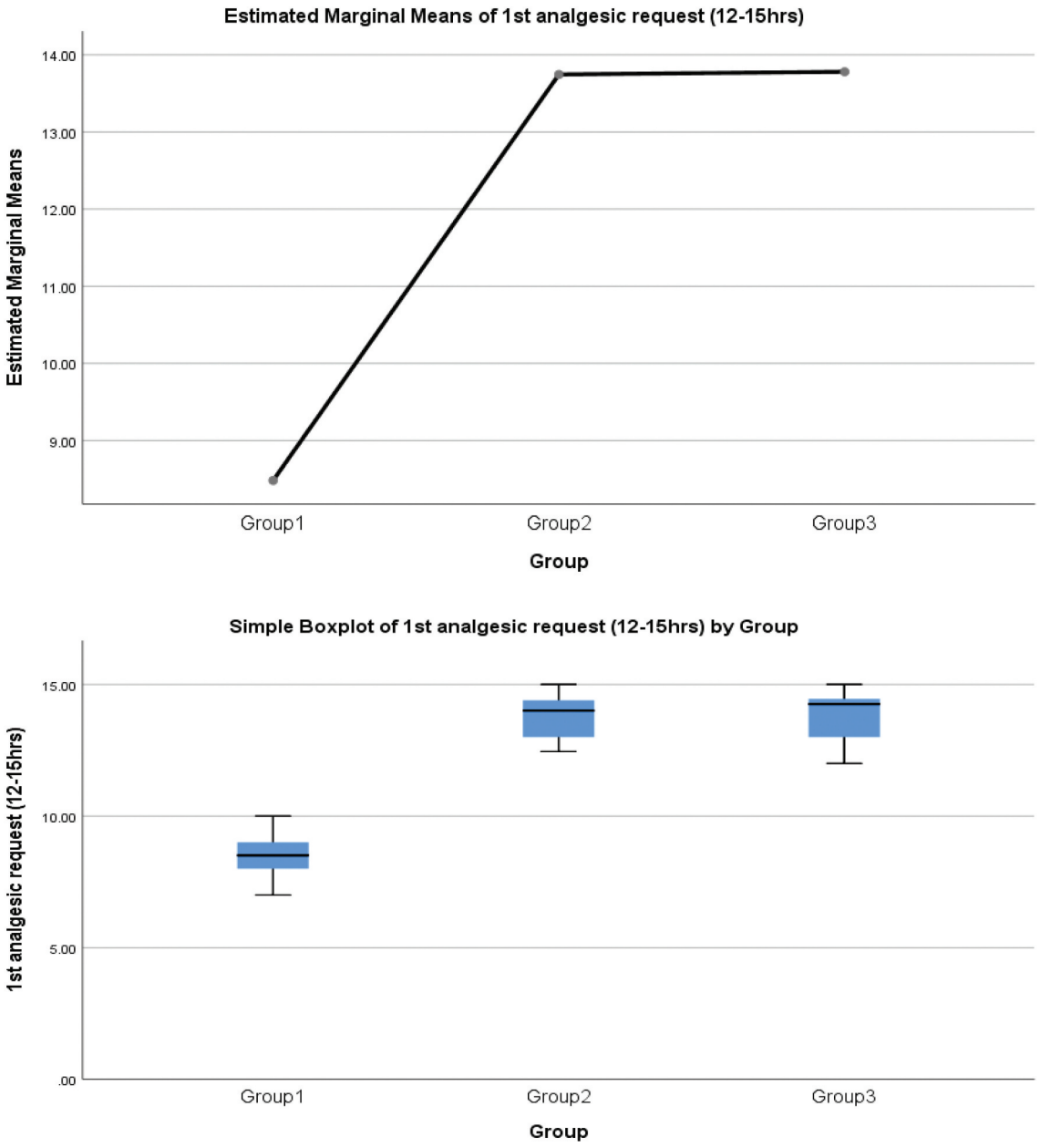


**Figure 4.** Estimated marginal mean and box plot of first analgesic request.

studies of Prasad D, et al. [47], Saraswathi C, et al. [48] and Tuteja S, et al. [49]., who agreed that the use of intrathecal magnesium sulfate resulted in a decrease in analgesic consumption during the first 24 hours after surgery when it is used with different kinds of operations.

According to our knowledge, our study is a pioneering at revealing the effect of using intrathecal $MgSO_4$ on decreasing sedation postoperatively in such surgeries as our results revealed that although $MgSO_4$ prolongs sedation intraoperatively, it decreases sedation scores postoperatively while increasing analgesic effect since it inhibits calcium ions from entering cells by blocking "N-methyl-d-aspartate" (NMDA) receptors. This analgesic effect is related to the prevention of central sensitization caused by peripheral tissue injury [50,51].

LANSS score was used to assess the chronic pain in the three groups. The results showed that the chronic pain in group (1) extended for more than 3 months after surgery. In groups 2 and 3 pain after the surgery did not last for more than 18 months. Sain A, et al [52] proved that the addition of MgSO4 to bupivacaine in epidural anesthesia has dual effects on the anaesthetic and analgesic profile [53].

Our study showed the superiority of magnesium sulfate over fentanyl in making patients feel less pain during the first 24 hours after surgery. It also showed better results in complications resulting from fentanyl anesthesia, as patients of groups (2) and (3) did not suffer from itching, nausea or dizziness. Nausea [54], vomiting [55] and itching [56] have been reported in many similar clinical trials.

Previous studies dealt with the effect of different concentrations of magnesium sulfate on hemodynamic, but with careful research, no other study, as far as we

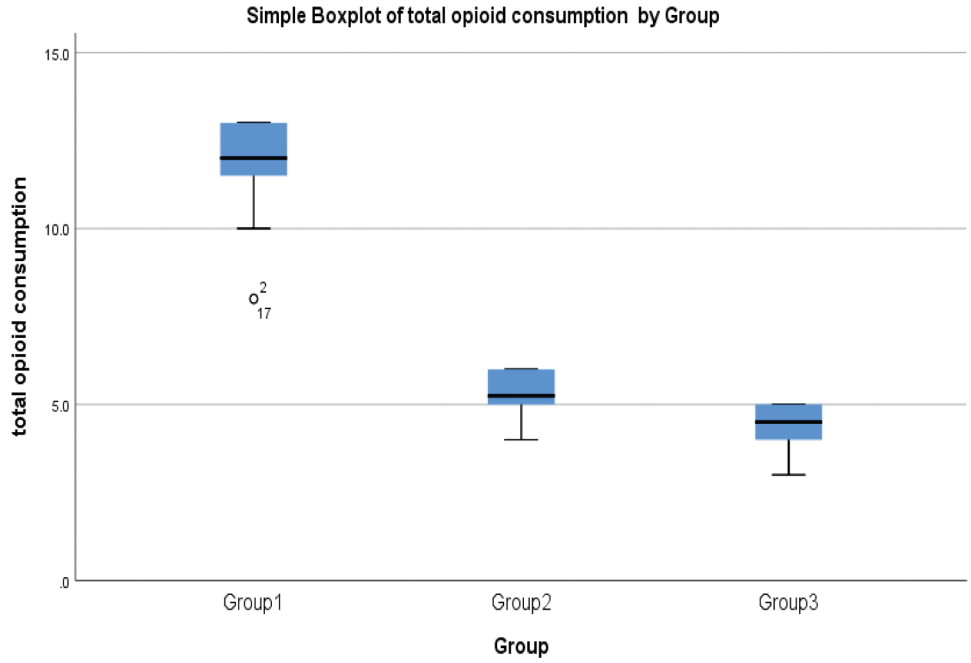


**Figure 5.** Box plot for total analgesic consumption.

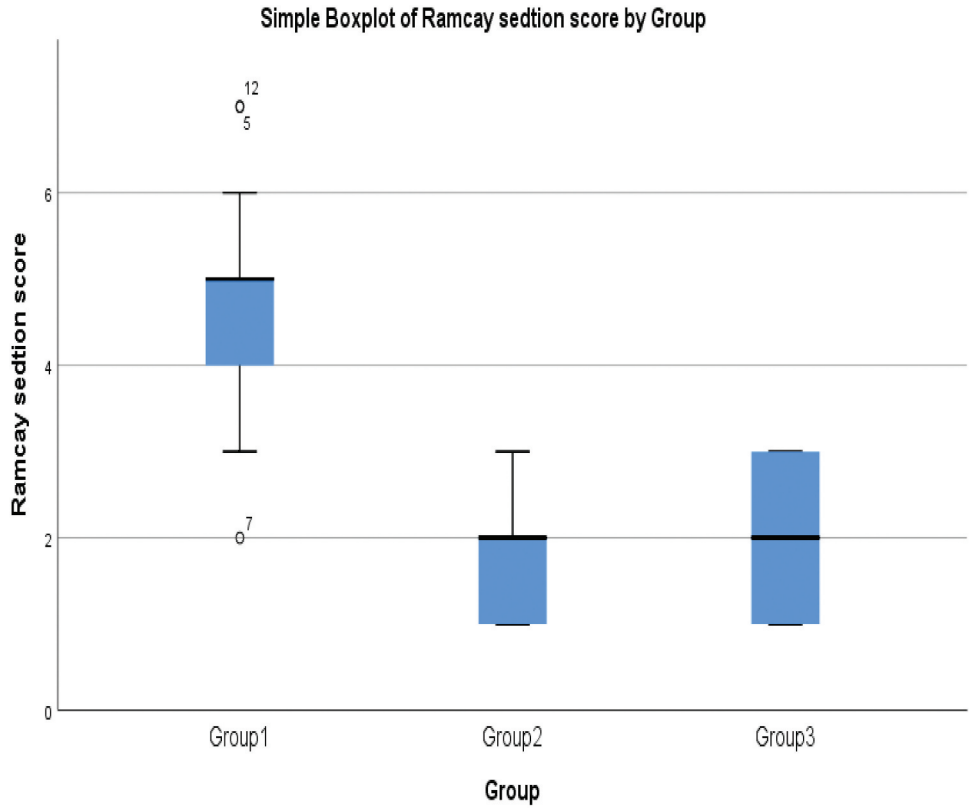


**Figure 6.** Box plot for Ramsay sedation score.

know, has dealt with the effect of different concentrations on complications for patients undergo pelvic surgeries; complications that have been recorded for the patients in group $MgSO_4$(100 mg) included vomiting, nausea, blurred vision and headache.

We think that our work has a number of limitations among which is the follow-up period is short, which could be extended for longer time in order to explore the ultimate duration of analgesia. The small sample size, although related to the nature of the disease, was not sufficient to powerfully investigate side effects. Finally, we recommend that further researches are required to evaluate the effect carefully.

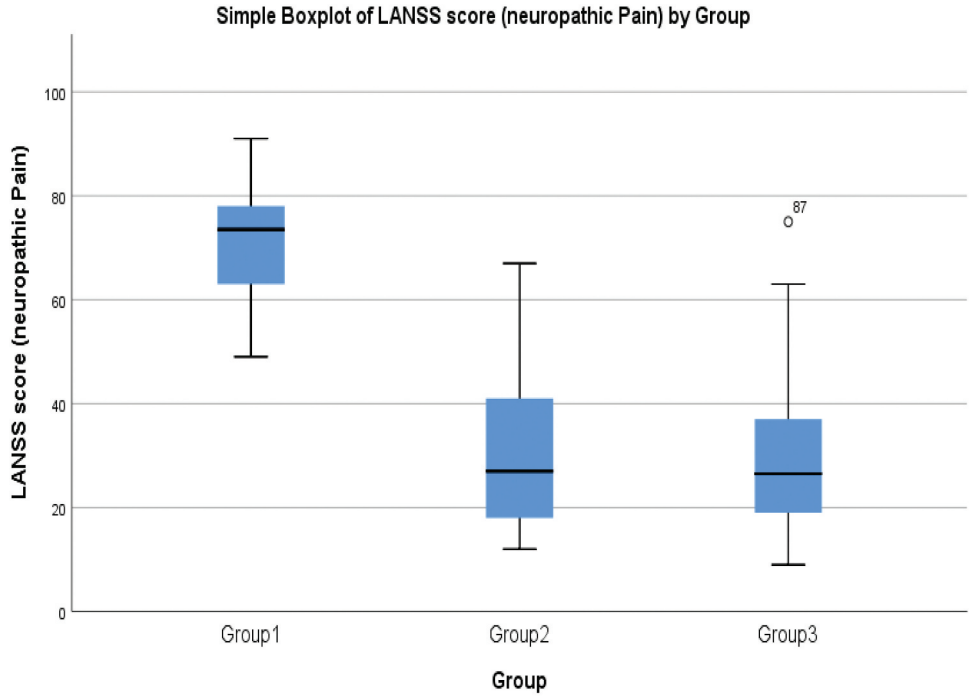


**Figure 7.** Box plot for LANSS score.

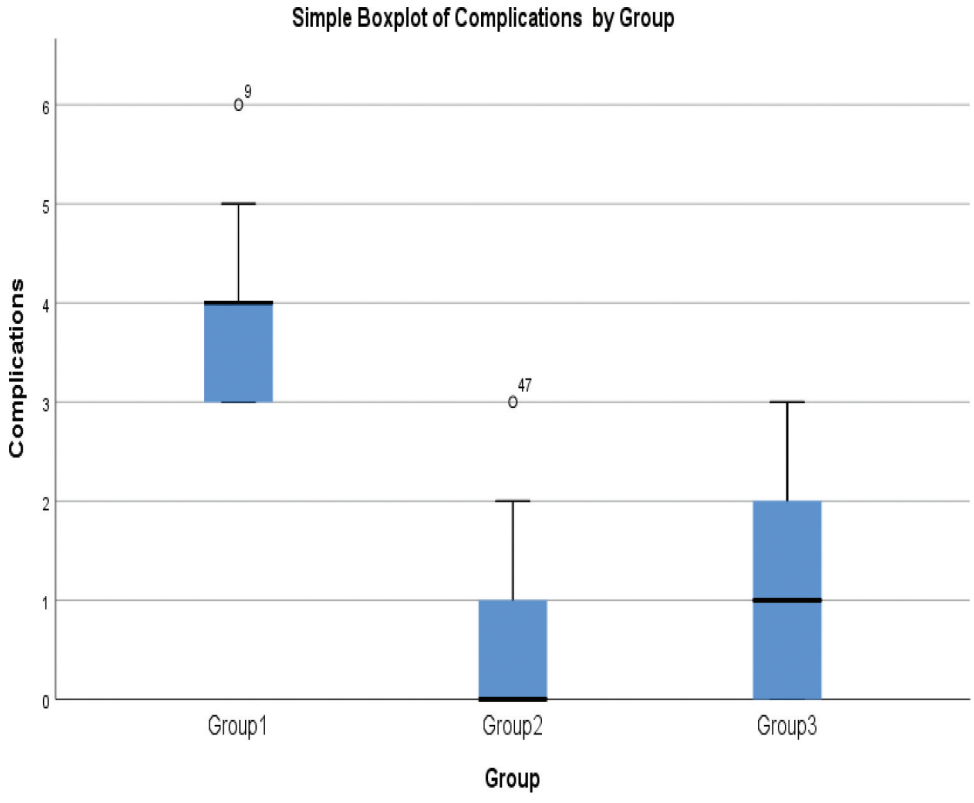


**Figure 8.** Box plot for complications in the three groups.

## 5. Conclusion

When comparing IT $MgSO_4$ at doses of 50 and 100 to fentanyl 50 mg, our study showed the superiority of magnesium sulfate over fentanyl in making patients feel less pain during the first 24 hours after surgery in pelvic and lower abdominal surgeries to excise tumors. We found that IT $MgSO_4$ 50 mg achieved a reasonable balance between postoperative analgesia and side effects.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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