

Comparing Gabapentin and Celecoxib in Pain Management and Complications After Laminectomy: A Randomized Double-Blind Clinical Trial

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Received 2015 November 18; Revised 2015 December 5; Accepted 2016 January 2.

Abstract

Background: Complications and postoperative pain are major care problems that can affect the quality of health care plan.

Objectives: According to the use of multimodal therapy the current study aimed to compare the efficacy of gabapentin and celecoxib in pain management and complications after laminectomy at Ilam University of Medical Sciences, Ilam, Iran, in 2015.

Patients and Methods: In this randomized double-blind clinical trial, 114 patients scheduled for elective laminectomy with simple random sampling design received gabapentin (n = 38, 900 mg/day), celecoxib (n = 38, 600 mg/day) and placebo (n = 38, capsule contain starch). Visual analog scale (VAS) was used to determine the intensity of pain. Complications after surgery, anxiety scores before surgery and patient's satisfaction 24 hours after the surgery were recorded.

Results: The mean pain intensity in the gabapentin group was lower compared to those of the placebo and celecoxib groups respectively at different time durations (P < 0.001). The means of morphine consumption were 11.9 mg, 22.8 mg and 30.1 mg in the gabapentin, celecoxib and placebo groups, respectively (P < 0.001). The prevalence of shivering, nausea, vomiting and pruritus were 10.5%, 12.8%, 10.3% and 18.4% in the gabapentin group vs 31.5%, 29.8%, 32.4% and 28.9% in the celecoxib group and 42.1%, 44.7%, 39.5% and 44.7% in the placebo group (P < 0.001). The mean anxiety score in the gabapentin group was 2.4 vs those of the celecoxib group 3 and placebo group 3.6 (P < 0.001). The frequencies of drowsiness were 42.1%, 13.2% and 5.3% in the gabapentin, celecoxib and placebo groups, respectively (P < 0.001). In the gabapentin group, patient satisfaction was significantly higher compared to those of the placebo and celecoxib groups (P < 0.05).

Conclusions: According to the effect of gabapentin on pain management, complications after laminectomy and increased patients satisfaction, it can be regarded as an alter native in multimodal analgesia.

Keywords: Multimodal Therapy, Analgesia, Laminectomy, Gabapentin, Celecoxib

1. Background

Postoperative pain causing several complications such as delay in wound healing, infections, prolong hospital stay, readmission after discharge, increase in morbidity and cost of hospital stay is one of the most common challenges in postoperative care process for physicians (1, 2). Therefore, management of post-surgical pain plays a critical role in the welfare of patients (3-5). Patients experiencing postoperative pain are exposed to decreased lung function and the risk of developing thromboembolism due to immobility, nausea and vomiting. Also cardiac workload, systemic vascular resistance, and myocardial oxygen consumption increase due to catecholamine release (6). The literature shows that 80% of the patients undergoing surgery, experience postoperative pain (1, 7); most (approximately 80%) of these patients reported moderate to severe pain intensity (8). Laminectomy fol-

lowing lumbar herniation is one of the most common surgeries with an incidence of 10% to 40% in neurosurgery. Annually, 300,000 to 400,000 lumbar surgeries are conducted (9); about 13,000 cases in the UK and over 250,000 cases in the US. In the United States alone \$2.5 billion is spent on lumbar surgery (10) and back pain annually causes loss of about 150 million days of work (11). Postoperative pain in these patients can continue for up to three days and 13% - 43% may cause chronic pain (12). Opioids are the first choice to treat pain after the surgery. The use of opioids due to a number of side effects such as respiratory depression, nausea, vomiting, excessive sedation, dizziness, drowsiness, pruritus, and urinary retention is limited (1, 12-15). Recently, there is emphasis on the use of non-opioid analgesic drugs (16, 17), the use of two or more analgesics, and multimodal therapy (1, 12).

One of these multimodal analgesia methods is the use of anti-epileptic drugs such as gabapentin (1) and other non-steroidal anti-inflammatory drugs (NSAID) such as celecoxib. Gabapentin is an anticonvulsant drug that has analgesic effect in post-herpetic neuralgia, diabetic neuropathy, and neuropathic pain. Celecoxib is one of the NSAIDs, that its analgesic effect is reported in various studies by cyclooxygenase-2 (COX-2) inhibitor (1, 18, 19).

2. Objectives

The current study aimed to investigate the comparative effect of gabapentin versus celecoxib on pain and complications after laminectomy based on the hypothesis that the effect of gabapentin and celecoxib on pain and complication after laminectomy are different.

3. Patients and Methods

It was a randomized double-blind clinical trial carried out at the Imam-Khomeini hospital (center of surgery and trauma) affiliated to Ilam University of Medical Sciences, Ilam, Iran, in 2015. This hospital is a teaching and academic hospital with a level 1 trauma center with 170 general beds and 12 intensive care unit (ICU) beds. The statistical population included all the patients referred to the department due to laminectomy.

3.1. Sample Collection

The sample size was calculated according to the data from a pilot study with 10 patients and the following formula:

$$(1) \quad n = (Z_1 + Z_2)2 \times (2S)2d2 = 38n$$

$Z_1 = 95\% = 1.96$; $Z_2 = 80\% = 0.84$ (test power); S , an estimate of the standard deviation of visual analog scale (VAS) in the groups; 1.67 in a pi-lot study; d , the minimum of the mean differences of VAS between the groups which showed a significant difference 1.1.

In the current randomized, double-blind clinical trial, there were 114 patients of grade I or II according to the American society of anesthesiologists (ASA), aged 20 - 60 years, scheduled for elective laminectomy under general anesthesia. Patients were randomized to three groups. In each group, there were 38 patients: group A (gabapentin), group B (celecoxib) and group C (placebo). A simple random sampling design was used (Figure 1). Sampling was performed with a sealed envelopes technique and coding. Coded as: code 1 = gabapentin, code 2 = celecoxib, code 3 = placebo. The patients, anesthesiologists and surgeons were blinded to the drug administered. Coding and sealed envelopes technique for the double-blind was prepared by a nurse who was not participating in the study.

3.2. Protocols

The patients in the group A (gabapentin) received 600

mg gabapentin two hours before surgery and 300 mg six hours after surgery, group B (celecoxib) received 400 mg celecoxib two hours before surgery and 200 mg six hours after surgery and group C (placebo) received a placebo capsule orally two hours before surgery and six hours after surgery. The patients with drug abuse, history of allergic reaction to any of the understudy drugs, under use of non-steroidal anti-inflammatory analgesic, pregnancy, cardiovascular, metabolic, respiratory, peptic ulcer and renal failure, or coagulation abnormalities were excluded from the study. The neurosurgeon and anesthesiologist were the same for all patients. Anesthesia was carried out with thiopentone (5 mg/kg IV), atracurium (0.5 mg/kg IV), and maintained with Isoflurane (1% - 1.5%) and nitrous oxide (50%) in oxygen. Fentanyl was given in the operation room according to the patient's need and clinical discretion. Patients were reversed with 0.05 mg/kg neostigmine combined with 0.02 mg/kg Atropine. Standard monitoring included electrocardiogram, noninvasive blood pressure, and pulse oximetry was done. In order to achieve the same VAS scores after surgery in the groups the extra morphine was used in the patients with pain in the placebo group.

3.3. Measurements

The VAS was used to determine severity of pain. The pain severity was assessed in the 2, 4, 6, 8, 12 and 24 hours after surgery. The patients' mean blood pressure (BP), heart rate (HR), respiratory rate (RR), saturation (SPO_2), urine retention, vomiting, shivering, headache, dizziness, nausea, drowsiness, pruritus and morphine consumption were recorded. Anxiety scores before surgery and patients' satisfaction 24 hours after surgery were recorded. Preoperative anxiety was assessed according to a seven-point scale (1 = relaxed, 2 = apprehension, 3 = mild anxiety, 4 = moderate anxiety, 5 = manifest anxiety, 6 = severe anxiety, 7 = very severe anxiety). The patients' satisfaction with pain management was assessed on a 5-point scale; 0 = poor, 1 = fair average, 2 = moderate, 3 = good and 4 = excellent) and recorded in postoperative periods. Shivering was assessed on a scale with 0 = no shivering observed; 1 = shivering observed (1).

3.4. Ethical Issues

The current study was approved by the vice chancellor for research at the Ilam University of Medical Sciences, Ilam, Iran (EC: 94/H/269); the informed consent was obtained from all subjects. This study was registered at the Iranian registry of clinical trials (IRCT2015071222870N3).

3.5. Validity and Reliability

VAS rating is a valid scale to evaluate pain severity with ratings from 0 to 10 (0 means no pain and 10 means the maximum pain in this scale). In order to determine the validity and reliability of the scale, content validity (content validity index (CVI) and content validity ratio (CVR)

and Cronbach's alpha test were used. The CVI and CVR indexes of the scale were 0.79 and 0.87 respectively. The reliability of the questionnaire was 0.83.

3.6. Statistical Analysis

Collected data were analyzed using the statistical software SPSS, ver.16. (SPSS Inc., Chicago, IL, USA). Descriptive statistics, the Chi-square test, one-way ANOVA, the Fisher least significant difference (LSD), Tukey test and repeated measurement were carried out to analyze the results. $P < 0.05$ was considered significant.

4. Results

Baseline characteristics of the patients are shown in Table 1. None of the 114 enrolled patients was withdrawn for any reasons. In the quantitative data according to Kolmogorov-Smirnov test, data distribution was normal and the parametric method was used ($P > 0.05$) Subjects characteristics were not different among the groups ($P > 0.5$) (Table 1). One-way ANOVA showed that the mean pain severity score in the gabapentin group was less than those of the placebo and celecoxib groups respectively at different intervals ($P < 0.001$) (Table 2).

According to LSD and Tukey test, the mean pain severity in the gabapentin group was significantly lower than those of the placebo and celecoxib groups respectively at various intervals ($P < 0.001$, $P < 0.05$). In the eighth hour after the intervention, although the mean pain severity in the celecoxib group was lower than that of the placebo group, no statistically significant difference between the two groups was observed ($P > 0.05$). Repeated measurement analysis showed that the mean pain score in the gabapentin ($P < 0.001$), placebo ($P < 0.05$) and celecoxib groups ($P < 0.05$) were significantly different in various intervals (Figure 2). The means of morphine consumption, anxiety score, shivering, nausea, vomiting and pruritus in the gabapentin group were significantly lower than those of the celecoxib and placebo groups respectively ($P < 0.001$, $P < 0.05$) (Tables 2 and 3, Figure 3). The frequencies of drowsiness (42.1%) in the gabapentin group were significantly higher than those of the celecoxib and placebo groups ($P < 0.001$). No statistically significant differences were observed between the groups in relation to headache and dizziness ($P > 0.05$) (Table 3), Patient satisfaction was significantly higher in the gabapentin group than those of the placebo and celecoxib groups ($P < 0.05$).

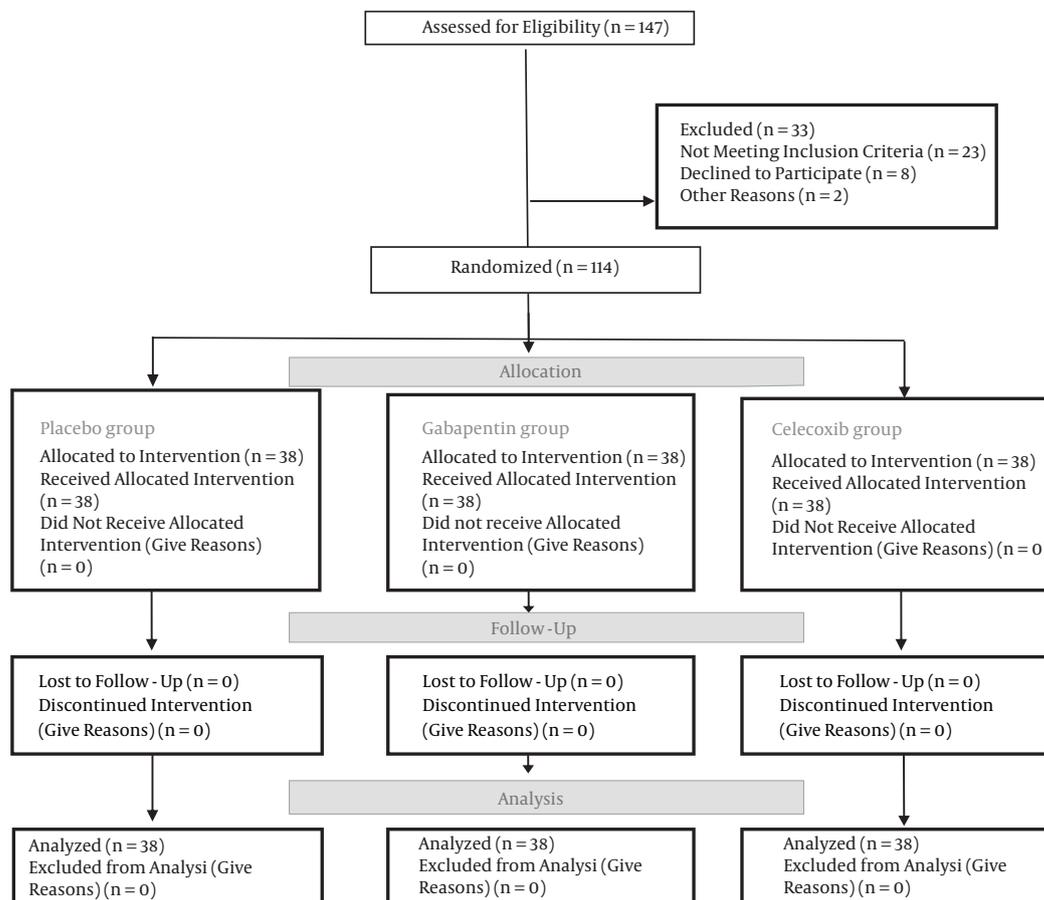


Figure 1. CONSORT Diagram of Participant in the Clinical Trial

Table 1. Baseline Characteristics of the Patients^{a,b}

| Characteristic | Placebo | Gabapentin | Celecoxib | P Value ^c |
|----------------------------------|-------------|-------------|-------------|----------------------|
| Age, y | 50.2 ± 7.2 | 49.5 ± 5.9 | 50.2 ± 4.2 | > 0.881 |
| Gender | | | | > 0.467 |
| Male | 28 (73.7) | 31 (81.6) | 29 (76.3) | |
| Female | 10 (26.3) | 7 (18.4) | 9 (23.7) | |
| Married | 34 (89.5) | 35 (92.1) | 36 (94.7) | > 0.871 |
| Duration of surgery, h | 2.11 ± 0.23 | 2.27 ± 0.28 | 2.17 ± 0.35 | > 0.654 |
| Duration of anesthesia, h | 2.35 ± 0.14 | 2.57 ± 0.18 | 2.49 ± 0.25 | > 0.537 |
| BP, mm/Hg | 132 ± 3.2 | 122 ± 3.6 | 126 ± 3.1 | > 0.863 |
| PR, per/min | 72.8 ± 3.4 | 73.6 ± 5.6 | 74.4 ± 5.4 | > 0.736 |
| Spo₂ | 95 ± 3.4 | 95 ± 2.2 | 96 ± 2.7 | > 0.741 |

Abbreviation: BP, blood pressure.

^aValues are expressed as mean ± SD unless otherwise indicated as No. (%).

^bN = 38.

^cP > 0.05.

Table 2. Severity of Pain, Morphine Consumption and Anxiety Score in the Groups^{a,b}

| Characteristic | Placebo | Gabapentin | Celecoxib | P Value |
|--|------------|------------|------------|-------------------|
| Pain score by vas at various intervals, h | | | | |
| 2 h after intervention | 7.6 ± 1 | 4.9 ± 0.7 | 6 ± 1 | 0 ^c |
| 4 h after intervention | 6.6 ± 0.9 | 3.8 ± 0.8 | 4.8 ± 0.5 | 0 ^c |
| 6 h after intervention | 5.4 ± 0.5 | 3.4 ± 0.5 | 4.4 ± 0.7 | 0 ^c |
| 8 h after intervention | 4.5 ± 0.6 | 3 ± 0.8 | 4.4 ± 1 | 0 ^c |
| 12 h after intervention | 2.9 ± 0.7 | 1.6 ± 0.5 | 2.5 ± 0.4 | 0 ^c |
| 24 h after intervention | 1.4 ± 0.4 | 0.7 ± 0.3 | 1 ± 0.4 | 0 ^c |
| Morphine consumption, mg | 30.1 ± 0.6 | 11.9 ± 4.4 | 22.8 ± 6.8 | 0 ^c |
| Anxiety score | 3.6 ± 0.7 | 2.4 ± 0.5 | 3 ± 0.9 | 0 ^c |
| Patient satisfaction | | | | |
| Good | 4 (10.5) | 19 (50) | 8 (21) | 0.03 ^d |
| Excellent | 0 (0) | 9 (23.6) | 3 (7.8) | 0.04 ^d |

Abbreviation: VAS, visual analog scale.

^aValues are expressed as mean ± SD unless otherwise indicated as No. (%).

^bN = 38.

^cP < 0.001.

^dP < 0.05.

Table 3. Frequencies of Adverse Effects Between the Groups^a

| Outcome Parameters | Placebo | Gabapentin | Celecoxib | P Value |
|------------------------|-----------|------------|-----------|--------------------|
| Vomiting | 15 (39.5) | 4 (10.3) | 12 (32.4) | 0.008 ^b |
| Shivering | 16 (42.1) | 4 (10.5) | 12 (31.5) | 0.004 ^b |
| Headache | 4 (10.5) | 5 (13.2) | 5 (13.2) | 0.930 ^c |
| Dizziness | 8 (21.1) | 13 (34.2) | 10 (26.3) | 0.519 ^c |
| Nausea | 17 (44.7) | 5 (12.8) | 11 (29.8) | 0.02 ^b |
| Drowsiness | 2 (5.3) | 16 (42.1) | 5 (13.2) | 0 ^d |
| Pruritus | 17 (44.7) | 7 (18.4) | 11 (28.9) | 0.04 ^b |
| Urine retention | 9 (23.7) | 5 (13.1) | 7 (18.4) | 0.637 ^c |

^aValues are expressed as No. (%).

^bP < 0.05.

^cP > 0.05.

^dP < 0.001.

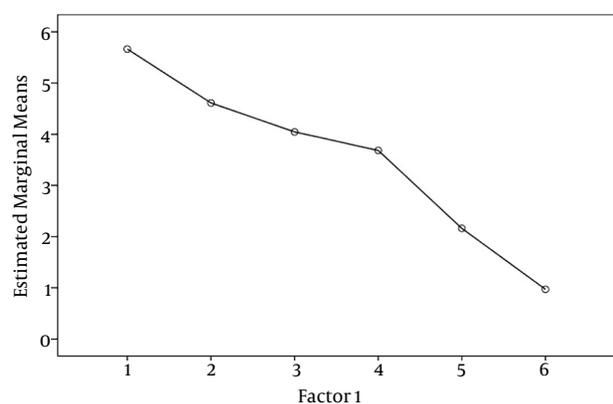


Figure 2. Repeated Measurement Analysis of Pain Between Groups

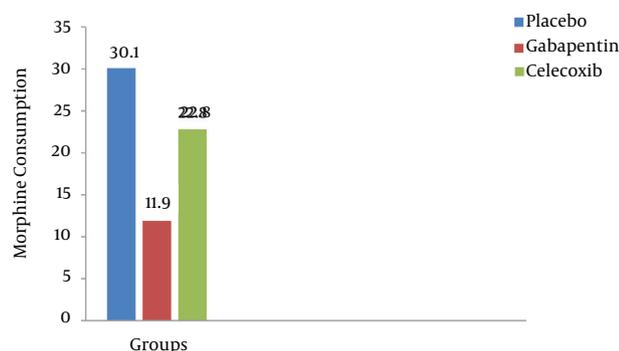


Figure 3. Morphine Consumption in the Groups

5. Discussion

In the past decade, despite the knowledge of pain physiology, about 80% of the patients after surgery experience postoperative pain (18). Postoperative pain, shivering, nausea, vomiting and urine retention are common complications impairing the quality of postoperative recovery such as readmissions after discharge, chronic pain after surgery and increasing morbidity and costs (8). Although opioids are the first choice to manage pain after surgery, they are associated with some complications (20). Recently, Interest in multimodal analgesia, using two or more analgesics and modalities with multi-mechanisms to treat analgesia and decrease the prevalence of complication is rising. One of these analgesia methods is the use of anticonvulsant drugs such as gabapentin and pregabalin (1). Therefore, the multimodal analgesic approach is recommended as an alternative treatment to manage postoperative pain (18). Management of pain after surgery and complications such as shivering and emesis are common challenges in care process and the basic principles in the early mobilization and the quality of postoperative care in the patients undergoing surgeries (5). The current study results suggested that

gabapentin versus celecoxib significantly reduced pain, overall morphine consumption, preoperative anxiety, pruritus, postoperative shivering, nausea and vomiting in patients following laminectomy under general anesthesia. Patient satisfaction was significantly higher in the gabapentin group compared to the placebo and celecoxib ones. This finding was consistent with the previous studies on the effects of gabapentin on postoperative pain and complications (21-24). A study by Ozgencil et al. (1) on 90 patients undergoing laminectomy found that gabapentin and pregabalin significantly reduced preoperative anxiety, pruritus, overall opioid consumption and postoperative shivering; patient's satisfaction was significantly higher compared to the placebo group. Kumar et al. (6) showed that after laminectomy, pregabalin significantly decreased pain compared to the placebo, but its impact was less than that of tramadol. Demand for morphine was less in tramadol group. In pregabalin group, the postoperative complications such as nausea, vomiting and drowsiness were less in comparison to those of the tramadol. In another study, Reuben et al. (18) concluded that following laminectomy, the patients in the pregabalin/celecoxib composition group had more analgesia and lower postoperative complications. In the study by Giancesello et al. (12) on the spinal surgery, pregabalin significantly decreased VAS scores, prevalence of constipation and emesis compared to the placebo group. Liporaci Juniot in the spinal surgery found that gabapentin significantly reduced the pain intensity after surgery (25). Rahimi et al. (26) concluded that daily consumption of 800 mg gabapentin can decrease the pain severity after laminectomy in the patients compared to the patients in the placebo group and the group that received 400 mg gabapentin daily. Studies emphasized on the use of non-opioid analgesic drugs and multimodal therapy to manage pain after surgery. Pain management, decreases in preoperative stress, reduced length of hospital stay and costs, increased patient's satisfaction, and a reduction in postoperative complications are the benefits of multimodal therapy (12). Pandey et al. (27) concluded that prophylactic gabapentin in patients undergoing laparoscopic cholecystectomy significantly decreased nausea and vomiting and fentanyl consumption. Syal et al. (28) in a study on patients undergoing open cholecystectomy found that gabapentin was effective on pain and morphine consumption reduction, but increased the prevalence of nausea and vomiting and sedation. Bafna et al. (29) in a study on patients undergoing elective gynecological surgeries under spinal anesthesia found that preemptive use of gabapentin and pregabalin significantly reduced the postoperative rescue analgesic requirement and increased the duration of postoperative analgesia. The sedation levels in the gabapentin group were significantly higher compares to those of the placebo and celecoxib groups. This finding suggests that gabapentin can raise the patients' sedation levels (1). Gabapentin, a structural feature of gamma amino butyric acid, is an an-

antiepileptic drug with known analgesic effects on diabetic neuropathy, post-herpetic neuralgia and neuropathic pain (19, 27). The mechanism of gabapentin action is to reduce the release of several excitatory neurotransmitters (e.g. glutamate, substance P, calcitonin, noradrenaline, gene-related peptide) by binding to the $\alpha 2\delta$ subunit of voltage dependent calcium channels (1, 30). Gabapentin has antiallodynic and antihyperalgesic properties that decrease the hyperexcitability of dorsal horn neurons due to tissue injury. Decreasing the central sensitization by gabapentin can decrease acute pain after surgery. Gabapentin can be decrease morphine consumption (31). The anxiolytic effects of gabapentin are reported in previous studies (1). On the other hand, the effect of gabapentin to treat nausea and vomiting in patients under cytotoxic therapy and patients under laparoscopic cholecystectomy is shown. The mechanism of gabapentin in the prevention of emesis due to decreases of tachykinin neurotransmitter activity is reported (27). Decrease of the severity of shivering is due to anticonvulsive, anxiolytic and analgesic effects of gabapentin (1). The limitations of the current research include relatively small sample size and the subjective perception of pain by patients. All patients enrolled in this study underwent surgery by a single surgeon; and the data were collected from a single center that was the strengths of this study. To conclude, the current study finding revealed that to manage the postoperative pain after laminectomy, gabapentin 900 mg/daily was the alternative in multimodal analgesia. It was observed that gabapentin had less adverse effects, decreased the amount of morphine consumption for postoperative pain management and increased patient satisfaction.

Acknowledgments

Authors thank Ilam University of Medical Sciences, patients and all people who participated in this study.

Footnotes

Authors' Contribution: Aminolah Vasigh and Javaher Khajavikhan participated in patient's anesthesia. Fatemeh Najafi, Molouk Jaafarpour and Ali Khani participated in the study design, control of patients and data analysis.

Funding/Support: This study was supported by Ilam University of Medical Sciences (EC: 94/H/269).

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