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Diclofenac Suppository vs. IV Acetaminophen Combined With IV PCA for Postoperative Pain Management in Patients Undergoing Laminectomy: A Randomized, Double-Blinded Clinical Trial

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Abstract

Background: Tissue damage caused by surgical procedures nearly always results in pain. The effective management of postoperative pain remains a challenge because of its influence on the surgical outcome and its critical role in early mobilization and functionality. Recent research on postoperative pain management supports a treatment approach known as "multimodal analgesia," which comprises the use of more than one method or modality of pain control and management.
Objectives: In the present study, we compared the effects of diclofenac suppository and intravenous (IV) acetaminophen combined with IV patient-controlled analgesia (PCA) for pain management after laminectomy surgery.
Patients and Methods: Our randomized, double-blinded controlled trial during 2013 at Besat hospital in Hamadan, Iran, included 102 ASA I-II patients aged 18 to 65 years who were candidates for laminectomy surgery. The patients were randomly assigned to receive the diclofenac suppository (100 mg) (n = 51) or IV acetaminophen (1 g in 100 mL normal saline) (n = 51) 10 minutes before completing surgery and 12 hours after the operation.
Results: The patients' characteristics were the same in both study groups. The patients' satisfaction levels were higher among those who received diclofenac when compared with the acetaminophen group, especially at the time points of 6 and 12 h after surgery. The consumed narcotic using the PCA pump within 24 h of surgery in the diclofenac group was significantly lower than that of the acetaminophen group (735.70 $\pm$ 59.61 μg vs. 819.70 $\pm$ 80.02 μg; $P < 0.001$).
Conclusions: The use of diclofenac suppository combined with IV PCA results in reduced narcotic usage and a higher level of patient satisfaction compared to the use of IV acetaminophen combined with IV PCA.

Keywords: Pain, Postoperative, Acetaminophen, Diclofenac, Analgesia, Patient-Controlled

1. Background

Tissue damage caused by surgical procedures nearly always results in pain. The effective management of postoperative pain remains a challenge because of its influence on the surgical outcome and its critical role in early mobilization and functionality. The impact of insufficient pain relief is well known to clinicians, and can be expected to result in delayed mobilization and related complications as well as psychological anxiety and distress. The relationship between analgesic technique and the immediate and remote postoperative consequences together with the overall success of surgery is not new, and postoperative pain assessment by means of the visual analogue scale (VAS) and opioid requirements are the main outcome variables in most studies (1-5).

Chronic post-operative pain is more common than realized, especially after specific types of surgery such as thoracotomy or mastectomy. The prognostic factors for developing continuing pain include preoperative pain, replication surgery, prolonged surgery, severe postoperative pain, surgical methods with a higher risk for nerve damage, chemotherapy or radiation, and some psychological and depressive disorder symptoms (6-8). It is not clear how successful preventative methods such as pre-emptive analgesia may be in preventing prolonged pain, but it is highly probable that early intervention (when early signs are first noticed) is more likely to be advantageous (7-12). Several studies have replicated previous results showing that severe acute postoperative pain is a risk factor for long-term adverse outcomes (13-17). These issues are particularly acute after major spine surgery, and adequate pain control

is therefore a challenge in patients undergoing these surgical procedures.

One of the imperative objectives of postoperative analgesia is opioid dose reduction to reduce both the side effects (e.g., nausea, vomiting, respiratory depression, itching, and ileus) and the subsequent sedation level, which leads to delayed patient mobilization and a longer hospital stay. Decreased opioid requirements can be achieved using a combination of analgesics of different pharmacological classes (1, 6-10).

Recent research on postoperative pain management supports a treatment approach known as "multimodal analgesia," which comprises the use of more than one method or modality for pain control and management (e.g., drugs from two or more classes) to achieve additive advantageous effects, to reduce side effects, or both (18, 19). Multimodal analgesia is actually a well-adjusted analgesia technique for postoperative pain management achieved through a multimodal approach with the synergistic effect of several analgesics and a consequent decrease in the associated side effects as a result of lower individual doses (1, 20-22). Non-steroidal anti-inflammatory drugs (NSAIDS) combined with opioids provide a favorable option for the effective management of postoperative pain; however, adverse effects and contraindications may limit their use (19, 23-25).

2. Objectives

In the present study, we aimed to compare the effects of diclofenac suppository and intravenous (IV) acetaminophen combined with IV patient-controlled analgesia (PCA) in the management of pain after laminectomy surgery and to achieve a reduction in opioid consumption.

3. Patients and Methods

We conducted a randomized, double-blinded controlled trial that included 102 (ASA I-II) patients aged between 18 and 65 years who were candidates for laminectomy surgery. The following exclusion criteria applied: patients who had used opioids within the 24 hours before surgery, patients whose surgery time exceeded 2.5 hours, or patients with underlying chronic diseases, a history of addiction, a sensitivity to NSAIDs and acetaminophen, a history of GI bleeding, or documented laboratory parameter impairments. The study protocol was approved by the local ethics committee of the University of Medical Sciences and was registered in Iran registry of clinical trials database under number: IRCT201311168768N3.

After written informed consent was signed by the patient or the patient's carer/parent, the participants were randomly assigned using a simple randomization procedure (computerized random numbers) to one of the two study groups to receive diclofenac suppository (D group) or IV acetaminophen (A group). Before the induction of anesthesia, routine monitoring procedures (i.e., ECG and pulse oximetry) were started and an IV line was inserted. General anesthesia was induced using thiopental (5 mg/kg), and anesthesia was maintained with 1% - 1.2% isofluran. Analgesics and relaxants were administered by continuous infusion at pre-established doses (fentanyl 2 μg/kg/h; atracurium 0.05 mg/kg/h) to the patients in both study groups (26-28).

The patients in group D received diclofenac suppository (100 mg) 10 minutes before the end of the surgery and 12 hours after the operation, while for the group A patients, IV acetaminophen (1 g in 100 mL normal saline) was infused at the same times. Both procedures were done by an anesthesia technician who was not involved in the study.

All the patients used the same model of disposable PCA pump (Accufuser Plus® P2015M; Woo Young Medical, Chungbuk, South Korea), which was programmed to deliver 2 ml/h fentanyl as a background infusion and 10 μg/mL per demand, with a 15 minutes lockout during a 24 hours period.

The study time points included H1 (after complete awareness at recovery), H6 (6 hours after completion of surgery), H12 (12 hours after completion of surgery), and H24 (24 hours after completion of surgery). At each time point, pain severity, sedation, and frequency of postoperative nausea and vomiting (PONV) were assessed and recorded for the two groups. The data collection was also done by independent staff not involved in the research. The visual analogue scale (VAS) was used to assess pain severity. In the case of pain with a score above 4, 4 mg of IV morphine was injected and recorded in the questionnaire. PONV was rated from 1 (without PONV) to 4 (severe PONV). Sedation level was assessed using the Ramsay sedation scale, which assesses arousability on six levels:

1) The patient is anxious and agitated/restless, or both;

2) The patient is cooperative, oriented, and tranquil;

3) The patient responds to commands only;

4) The patient shows a brisk response to light or loud auditory stimulus;

5) The patient shows a sluggish response to loud auditory stimuli;

6) The patient exhibits no response.

In the case of a sedation score above 3, IV PCA was put on hold and the patient was monitored.

In the case of respiratory depression, which is defined as a respiratory rate of less than 10 breaths per minute, immediate cessation of IV PCA and the administration of IV naloxone 40 μg was performed. The patient satisfaction

levels were ordinally scaled as low, intermediate, high, and very high.

The results were presented as mean ± standard deviation (SD) for the quantitative variables and summarized by frequency (percentage) for the categorical variables. The continuous variables were compared using a t-test or a non-parametric Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the two study groups. The categorical variables, on the other hand, were compared using a chi-squared test or Fisher's exact test when more than 20% of the cells with an expected count of less than 5 were observed. The trend of the changes in the study variables within the study period was assessed using the repeated measures ANOVA test. For the statistical analysis, the statistical software SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

4. Results

In this study, 102 patients were randomly assigned to two groups: the patients in group D received diclofenac suppository (n = 51) and those in group A received IV acetaminophen (n = 51). No statistically significant differences were observed in the demographic characteristics (sex, age, and weight) and the duration of the surgery between the two study groups (P > 0.01) (Table 1).

Table 1. Mean Patient Age and Weight, and Duration of Surgery for the Diclofenac and Acetaminophen Groups

Variable	Study Group		P Value
	Diclofenac	Acetaminophen	
Age, y	44.11 ± 10.19	42.65 ± 9.99	0.462
Weight, kg	70.06 ± 9.34	68.63 ± 9.82	0.464
Duration of surgery, h	1.18 ± 0.35	1.19 ± 0.36	0.14

The pain scores between the two study groups at the different time points showed no statistically significant differences (Table 2), and pain severity gradually reduced 24 hours after surgery. The patient satisfaction levels were significantly higher among those who received diclofenac than acetaminophen, especially at the time points of 6 and 12 hours after surgery (P < 0.001) (Table 2).

No significant differences were found in the prevalence of PONV between the two study groups at the different time points during the first 24 hours after surgery (Table 3). A similar status was observed when comparing the sedation scores between the two groups (Table 3). There

Table 2. Comparison of the Pain and Patient Satisfaction Scores, and the Consumed PCA Opioid Between the Diclofenac and Acetaminophen Groups in the First 24 Hours After Surgery[a]

Time/Variable	Study Group		P Value
	Diclofenac	Acetaminophen	
During recovery			
Pain score	9.87 ± 2.9	7.44 ± 2.3	0.187
Satisfaction	2.94 ± 0.72	2.8 ± 0.7	0.36
After 6 h			
Pain score	3.35 ± 1.55	4.46 ± 1.2	0.34
Satisfaction	3.63 ± 0.53	3.27 ± 0.8	0.009
After 12 h			
Pain score	3.25 ± 1.07	2.98 ± 1.2	0.331
Satisfaction	3.94 ± 0.24	3.74 ± 0.56	0.02
After 24 h			
Pain score	1.5 ± 0.96	1.76 ± 0.8	0.14
Satisfaction	3.98 ± 0.14	3.88 ± 0.44	0.12
Consumed fentanyl, μg	735.48 ± 59.61	819.7± 80.02	< 0.001
Consumed morphine, mg	6.2 ± 1.7	5.9 ± 1.2	0.18

[a]The pain scores were measured using the visual analogue scale (0 - 10), and patient satisfaction was measured using an ordinal scale (1 = weak; 2 = moderate; 3 = good; 4 = excellent).

was however a significant difference in the consumed narcotic used via the PCA pump within 24 hours of surgery between the diclofenac and acetaminophen groups (735.70 μg ± 59.61 vs. 819.70 μg ± 80.02, respectively) (P < 0.001) (Table 3). The total amount of morphine used by the two groups was compared, and a statistical analysis revealed no significant difference between the two groups.

No major adverse events like respiratory depression, severe drowsiness, and abnormal bleeding were observed, and there was therefore no need for naloxone administration.

5. Discussion

Opioids can produce a strong analgesic effect by triggering the opioid receptors on the peripheral sensory neurons. Inflammation makes a number of cellular courses that result in a higher concentration of opioid receptors at the peripheral nerve terminals. This, as well as other alterations in intra- and extracellular mechanisms, leads to the increased antinociceptive effectiveness of peripherally administered opioids in inflamed tissue (20).

Nevertheless, opioid analgesics, which are considered the standard approach to preventing acute postoperative

Table 3. Comparison of the PONV and Sedation Scores Between the Diclofenac and Acetaminophen Groups in the first 24 Hours After Surgery[a]

	Study Group		P Value
Time/Variable	Diclofenac	Acetaminophen	
In recovery			
PONV	1.38 ± 0.59	1.33 ± 0.24	0.70
Sedation score	2.12 ± 0.62	2.22 ± 0.7	0.36
After 6 h			
PONV	1.31 ± 0.64	1.33 ± 0.59	0.83
Sedation score	2.08 ± 0.24	2.06 ± 0.31	0.009
After 12 h			
PONV	1.13 ± 0.44	1.24 ± 0.74	0.40
Sedation score	2 ± 0.01	2.04 ± 0.28	0.02
After 24 h			
PONV	1.08 ± 0.33	1.08 ± 0.35	0.95
Sedation score	2 ± 0.01	2.1 ± 0.01	0.12

[a] Postoperative nausea and vomiting (PONV) was measured using an ordinal scale (0 = no nausea; 1 = mild nausea without vomiting; 3 = mild nausea and vomiting; 4 = severe nausea and vomiting), and sedation scores were measured using the Ramsay sedation scale.

pain, can be substituted by a combination of opioid and nonopioid analgesic medicines with miscellaneous methods of action as part of multimodal analgesia. The practice of multimodal analgesia is rapidly becoming the "standard of care" for preventing postoperative pain and delivering higher pain relief with reduced analgesic-related adverse effects (21).

In our study different modules of analgesics (i.e., opioids, NSAIDs, and paracetamol) were used as part of the multimodal analgesia. According to our findings, the use of diclofenac suppository leads to higher levels of patient satisfaction and decreased opioid (fentanyl) consumption by PCA pump compared to the use of IV acetaminophen combined with IV PCA.

In one study, the authors analyzed data from 52 randomized placebo-controlled trials (4,893 adults) that tested acetaminophen, NSAIDs, or selective cyclooxygenase-2 inhibitors given in combination with morphine after surgery (29). The mean 24 hours morphine consumption was significantly reduced in all regimens by 15% - 55%, but only the NSAIDs resulted in decreased pain intensity at 24 hours (1 cm on the 0 - 10 cm VAS), nausea/vomiting, and sedation in this study. The authors therefore concluded that the combination of NSAIDs with patient-controlled analgesia morphine offers some benefits over morphine alone, which was consistent with our study's results.

In another study conducted by Dhawan et al. (30), 37 adults undergoing elective coronary artery bypass grafting surgery were randomly assigned in a double-blind clinical trial to receive either rectal diclofenac 100 mg or a placebo suppository. The 24 hours consumption of tramadol in the diclofenac group was significantly lower than in the placebo group (92.5 ± 33.5 mg vs. 157.5 ± 63.4 mg, P = 0.002), which was also consistent with our findings. The patients in the placebo group had more postoperative nausea and meaningfully higher pain scores 1.5 - 12 hours after extubation.

In a study by Kuzucuoglu et al. (31), patients were randomly assigned to receive intramuscular diclofenac or IV paracetamol. Although the mean dose of the consumed narcotic was similar in both study groups, the differences in the pain and Ramsay sedation scores were considered significant between the two groups, so the authors concluded that both paracetamol and diclofenac have the same analgesic effects and could be used safely in combination with morphine (31). Although the mean pain scores in the diclofenac group were lower at different time points in our study, we did not find a significant difference in either the pain or sedation scores between the two study groups. Notwithstanding, the difference between the mean doses of the consumed fentanyl in the PCA pump was significantly lower in the diclofenac group.

In another study by Ural et al. (32), a comparison between oral, IV, and intramuscular diclofenac led to lower pain and sedation scores. Additionally, research by Darvish et al. (33) revealed that the combination of diclofenac and paracetamol is much more effective than meperidine in reducing pain and the total required analgesics after cesarean section delivery (33).

In a systematic review in 2012, Sharma et al. (34) showed a lack of evidence for the overall benefits of most regional analgesic methods, gabapentinoids, and most NSAIDs on postoperative pain after spine surgery. Although the discrete advantage of each of these compounds was limited, the total benefit could only be shown when they were combined, so future research studying the effects of intensive and extended multimodal analgesic interventions was proposed.

Nonetheless, this randomized controlled trial had several limitations. First, the total number of cases included in the study was too low to indicate conclusive results. Second, the primary risk factors of PONV, like a prior history of motion sickness and/or PONV and being a non-smoker, were so difficult to establish in the literature that we decided not to include these as evaluation items. We also did not conduct long-term follow-ups of the patients to evaluate possible chronic pain, which serves as a further limitation of the study. Therefore, more multicenter randomized

controlled studies, which could include different kinds of patients and various doses or routes of administration for specific surgeries and non-surgical treatments or anesthesia, should be designed reasonably to confirm and certify the results achieved in the present study.

According to our study findings, the use of intravenous paracetamol or diclofenac suppository combined with a fentanyl PCA pump leads to good postoperative analgesia, but it seems that because of the higher levels of patient satisfaction and the reduction in total opioid consumption, diclofenac suppository provides superior analgesia by far.

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Footnote

Authors' Contribution: Mahshid Nikooseresht had primary responsibility for protocol development, patient screening, enrollment, outcomes assessment, preliminary data analysis, and writing the manuscript. Mohammad Ali Seifrabiei and Maryam Davoodi participated in the development of the protocol and the analytical framework for the study and contributed to the writing of the manuscript. Mashhood Aghajanlou contributed to the development of the protocol and the analytical framework for the study and the writing of the manuscript, and was responsible for patient screening. Mohammad Taghi Sardari supervised the design and execution of the study, performed the final data analyses, and contributed to the writing of the manuscript.

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