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The Effects of Phenyramidol and Diclofenac Treatment on Fracture Healing in Rats

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Background: Fracture healing or nonunion refers to a process in which many factors interact. In this study, we aimed to evaluate the radiological, histological, and biomechanical effects of phenyramidol and diclofenac, which are frequently used to treat post-fracture ture pain worldwide, on fracture healing and nonunion in a rat femur fracture model.

Methods: In this study, 72 male Wistar-Albino rats aged 2–3 months and weighing 250 ± 30 g were divided into 4 main groups. The rats were divided into 12 subgroups according to the early, middle, and late periods. A fracture model was created in rat femurs, and surgical fixation was performed. Postoperative analgesic treatment protocols included phenyramidol, diclofenac, phenyramidol + diclofenac, and the control group. The rats were sacrificed on the fifteenth, thirtieth, and forty-fifth days and were evaluated radiologically, histopathologically, and biomechanically.

Results: Scoring was conducted independently by 2 orthopedists not involved in the study. When the results were analyzed statistically, no statistically significant difference was observed between the fifteenth and thirtieth day radiology score values of the control, diclofenac, phenyramidol, and Phenyramidol + diclofenac groups ($p > 0.05$), but there was a statistically significant difference ($p < 0.05$) between the forty-fifth day radiology score values of the control, diclofenac, phenyramidol, and phenyramidol + diclofenac groups.

Conclusions: Our study shows that the use of diclofenac or phenyramidol alone negatively affects postoperative fracture healing. However, this effect was less pronounced in the combined treatment group. Histologic examination revealed that neither treatment had a significant effect on healing. There were statistical differences in biomechanical and radiologic properties between the phenyramidol and diclofenac groups; in particular, the diclofenac group had lower biomechanical properties.

Keywords: *Fracture healing, Phenyramidol, Diclofenac, Rat*

Fracture healing occurs after the interrelated processes of many biochemical and cellular pathways. Many factors positively and negatively affect fracture healing through these processes. Currently, with a better understanding of the pathophysiology of fracture healing, many innovative treatment methods have been used to shorten the fracture healing time and minimize nonunion problems. There are many treatments and physical and biological therapy methods that affect different steps of this process.[1] In addition to fracture healing, coping with pain is an important problem in fracture treatment. When patients who underwent surgery after fracture were analyzed, the majority of patients needed analgesic treatment during the preoperative and postoperative periods. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat pain, fever, and inflammation since the nineteenth century and are among the most widely used drugs worldwide.[2]

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NSAIDs play an important role in the treatment of fracture-related pain and comorbidities. They can also be used in the prevention of fracture complications in the long term. NSAIDs play a very important and valuable role in the treatment of fractures, but they are still the subject of research due to their possible adverse effects on fracture healing. There are many studies on NSAIDs in the literature. However, differences in the drugs used, as well as their duration and dosage, can influence their effects on bone quality. A review of the literature revealed that there is no consensus on the use and safety of these drugs; new studies are needed, or new types of analgesics may be needed during the postoperative period instead of these drugs.[3,4]

Currently, muscle relaxants are being used as frequently as NSAIDs in the preoperative and postoperative periods for the treatment of fractures. In some studies, it has been reported that some muscle relaxants have anti-inflammatory, analgesic, and anti-edema effects similar to those of nonsteroidal anti-inflammatory drugs.[5,6] Due to the lack of consensus on the use of NSAIDs, the fact that some muscle relaxant drug groups have similar effect profiles to NSAIDs in recent studies and the lack of consensus led us to design this study. The active ingredient of phenyramidol, muscle relaxant, and the active ingredient, diclofenac, NSAID, can be used as analgesics during the postoperative period due to their analgesic effects. The negative effects of NSAIDs on fracture healing are still controversial and NSAIDs are frequently used in trauma treatment in fracture patients. The efficacy and side effects of new molecules are important in this regard and should be investigated.[7] In our experimental animal model study, we investigated the effects of phenyramidol and diclofenac on fracture healing in a rat femur closed fracture model.

METHODS

After obtaining the necessary permission from the Duzce University Duzce Medical Faculty Experimental Animals Local Ethics Committee (2023/03/14), the study was conducted at the Duzce University Duzce Medical Faculty Experimental Animals Application and Research Centre Laboratory. In this study, principles of laboratory animal care were followed. The animals used in the study were sourced from the Duzce University Experimental Animals Research and Application Center.

Study Design

Seventy-two male Wistar-Albino rats were used in this study. Male Wistar rats (n = 6) aged 2–3 months and weighing 250 ± 30 g were kept in the laboratory at a room temperature of 23 ℃, humidity of 60% ± 5%, and a 12:12 light–dark cycle. Food and water intake were freely available. The study was performed by forming 12 equal groups with 6 animals in each group. During the study, the rats were given unlimited tap water (ad libitum) and standard rodent feed. The animals were caged in a room with a controlled temperature (23 ℃ –25 ℃) and a 12:12 hours light/dark cycle. No antibiotic prophylaxis was administered to any group before, during, or after the intervention. No animals died during the study period. No wound site infection was observed in any of the rats during follow-up. The animals used in the study were administered ketamine and xylazine via the intraperitoneal route before the surgical procedure. After the operation, 72 rats were randomly divided into 12 groups of equal numbers (Table 1). At the end of the study, the subjects were euthanized by cervical dislocation under anesthesia, and the femur bones were dissected. After the rats were euthanized, their left femurs were disarticulated from the hip and knee joints. The soft tissues on the femur were gently removed from the bone without damaging the callus tissue. All femurs were examined radiologically, biomechanically, and histologically.

Surgical Procedure

The rats were taken to the intervention room after the necessary monitoring and preparations were made. The weight of each rat was determined with an electronic scale, and the anesthetic dose was calculated. Ketamine (Eczacıbaşı) 50 mg/kg and Xylazinne (Bayer) 10 mg/kg in combination were used as anesthetics. Anesthesia was administered intraperitoneally in the right groin region.

Table 1. Group Characteristics of the Subjects

Group	Group 1 (a, b, c)	Group 2 (a, b, c)	Group 3 (a, b, c)	Group 4 (a, b, c)
Number of rats	18	18	18	18
Treatment duration (day)	15	15	15	15
Tracking time (day)	a, 15; b, 30; c, 45	a, 15; b, 30; c, 45	a, 15; b, 30; c, 45	a, 15; b, 30; c, 45

The left thighs of the rats were shaved and stained with povidone iodide (Batticon, ADEKA) (Fig. 1). After osteotomies were created in all groups, both fracture ends were held by clamps. A 1.2-mm Kirschner wire (Tıpmed) was inserted intramedullary into the distal fragment before the fracture line, exiting the knee joint. Afterwards, the motor tip was attached to the side of the Kirschner wire exiting the knee joint, and after the fracture was reduced, the Kirschner wire was advanced intramedullary to the femoral proximal to the cortex. The wire remaining in the canal was cut at the level of the femoral condyles so as not to protrude from the condyle. The wire end was left under the skin. The skin was closed with 2/0 silk. The wound site was wiped with povidone iodide, and the rat was removed from the operating table. The animals were placed in cages in groups of 6, and group names were written. Following clinical examination, the fracture and fixation were confirmed radiologically by direct radiography (Fig. 2).

Histopathological Evaluation

Soft tissues covering all fractured femurs were stripped without removing the periosteum, and the K-wire was carefully removed without damaging the callus tissue. Before decalcification in 7% formic acid, the femurs were fixed in 4% paraformaldehyde at 4 °C for 48 hours.

After decalcification, the samples were embedded in a paraffin block, and 7-μm sections were cut. The sections were stained with hematoxylin and eosin dye. Fracture healing was evaluated histopathologically using the scoring system proposed by Huo et al.[8]

Radiological Evaluation

Anteroposterior and lateral femur radiographs were taken on the fifteenth, thirtieth and forty-fifth days for all sacrificed rats. Lane and Sandhu's grading system was used for radiological scoring.[9] Scoring was conducted independently by 2 orthopedists not involved in the study.

Biomechanical Evaluation

Biomechanical analyses were performed on 72 rat femurs sacrificed from group 1, group 2, and group 3 on days 15, 30 and 45. Biomechanical analyses were performed on sacrificed rat femurs on the same day without holding. The intramedullary fixation material was removed before biomechanical testing. Biomechanical analyses were performed using a BMT-E Series material testing machine (Besmak) at Duzce University Scientific and Technological Research Application and Research Centre. A 3-point bending test was applied for biomechanical evaluation (Fig. 3). Before the femurs were placed horizontally on the test device, the widest possible distance between the 2 support points was set to 18 mm for all femurs, taking into account the femur length. Afterwards, the bending force was applied at a speed of 3 mm/min, coinciding with the fracture line at the midline. The force applied to the fracture line was increased until the resistance was broken, and the highest force (in Newtons) observed in the device just before the fracture was recorded for each specimen. These recorded measurements were used for biomechanical evaluation.

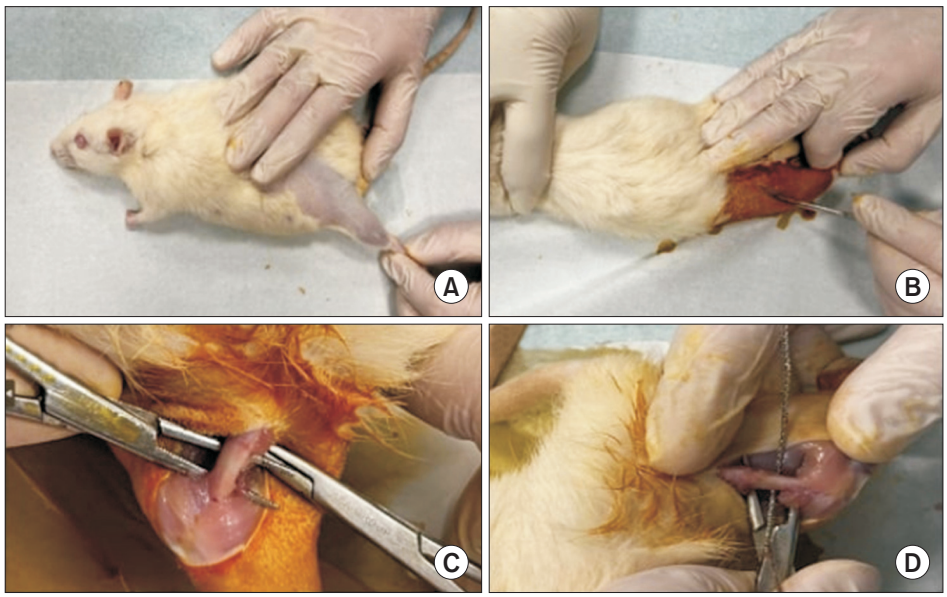

Fig. 1. Surgical technique. (A) Preparation of the thigh area by shaving before surgery. (B) Opening a skin incision from the lateral thigh. (C) The femoral shaft was exposed by blunting the muscles. (D) Osteotomy application using a Gigli wire.

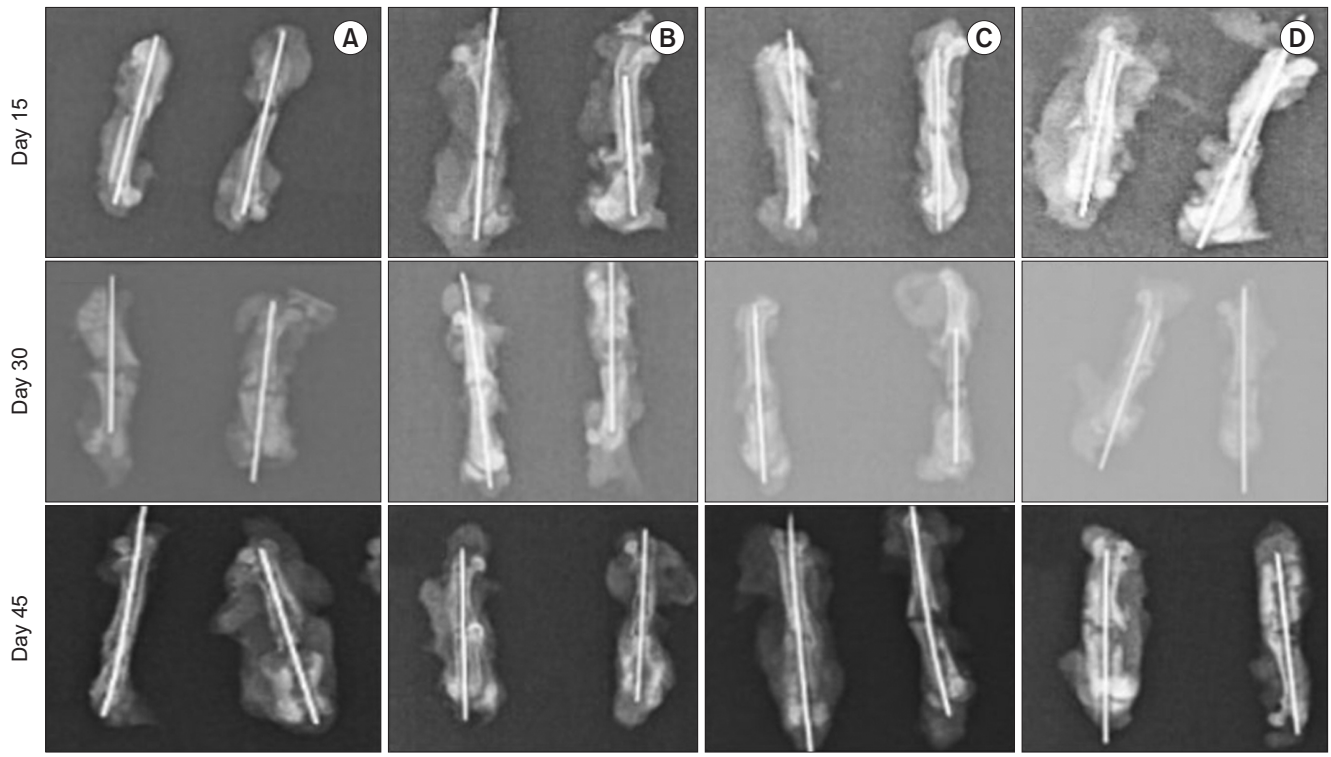

Fig. 2. Postsurgical radiological images. (A) Phenyramidol group. (B) Diclofenac group. (C) Phenyramidol + diclofenac group. (D) Control group.

Fig. 3. Three-point bending test application for biomechanical analysis.

Statistical Analysis

In this study, statistical analyses were performed with the National Cancer Genome Atlas (NCSS) (Number Cruncher Statistical System) 2007 Statistical Software package. Data were evaluated using descriptive statistical methods such as mean, standard deviation, median, and interquartile range, as well as the distribution of the variables with the Shapiro-Wilk normality test, paired one-way analysis of variance in time comparisons of variables showing a normal distribution, one-way analysis of variance in intergroup comparisons, the Friedman test in time comparisons of variables not showing a normal distribution, and the Kruskal-Wallis test in intergroup comparisons. The results were evaluated at the level of significance ($p < 0.05$).

RESULTS

Histopathological, radiological, and biomechanical scoring between the groups are given in Table 2. According to Table 2, no statistically significant differences were observed between the day 15, day 30, and day 45 pathology score values of any of the groups ($p = 0.571$, $p = 0.743$, and $p = 0.878$), and no statistically significant differences were observed between the day 15 and day 30 radiology score values of the groups ($p = 0.227$ and $p = 0.055$). The radiology score of the control group was significantly greater than that of the other groups ($p = 0,005$, $p = 0,014$, and $p = 0,027$); the radiology score of the phenyramidol + diclofenac group was significantly greater than that of the diclofenac and phenyramidol groups ($p = 0.043$ and $p = 0,048$); and no statistically significant difference was observed between the diclofenac and phenyramidol groups ($p = 0.784$).

As shown in Table 2, a statistically significant difference was observed between the fifteenth day biomechanical values of the groups ($p = 0.001$). The biomechanical in-

Table 2. Examination of Histopathology, Radiology, and Biomechanics Scores

Score		Control group	Diclofenac group	Phenyramidol group	Phenyramidol + diclofenac group	*p*-value
Pathology score						
15 Days	Mean ± SD	7.5 ± 0.84	7.67 ± 1.51	6.67 ± 2.42	8.17 ± 1.17	0.571*
	Median (IQR)	7 (7–8.25)	7 (6.75–9.25)	7 (5.5–8.25)	8 (7–9.25)	
30 Days	Mean ± SD	8 ± 0.63	8.33 ± 0.82	8.33 ± 0.52	8.33 ± 0.82	0.743*
	Median (IQR)	8 (7.75–8.25)	8.5 (7.75–9)	8 (7.75–8.75)	8.5 (7.75–9)	
45 Days	Mean ± SD	7.17 ± 3.13	8 ± 0.63	8.17 ± 0.75	7.83 ± 0.75	0.878*
	Median (IQR)	8 (6.25–8.5)	8 (7.75–8.25)	8 (7–8.5)	8 (7–8.25)	
p-value‡		0.504	0.058	0.101	0.717	
Radiology score						
15 Days	Mean ± SD	0.83 ± 0.41	0.33 ± 0.52	0.67 ± 0.52	0.33 ± 0.52	0.227*
	Median (IQR)	1 (0.75–1)	0 (0–1)	1 (0.5–1)	0 (0–1)	
30 Days	Mean ± SD	2 ± 0.89	1.5 ± 0.55	0.83 ± 0.41	1.33 ± 0.52	0.055*
	Median (IQR)	2 (1–3)	1.5 (1–2)	1 (0.75–1.25)	1 (1–2)	
45 Days	Mean ± SD	3.83 ± 0.41	2.5 ± 0.55	2.5 ± 0.84	3.17 ± 0.41	0.007*
	Median (IQR)	4 (3.75–4)	2.5 (2–3)	3 (2–3.25)	3 (3–3.25)	
p-value‡		0.005	0.005	0.003	0.004	
Biomechanics						
15 Days	Mean ± SD	44.89 ± 1.4	49.7 ± 9.48	53.87 ± 10.19	25.21 ± 8.11	0.001†
30 Days	Mean ± SD	55.63 ± 14.03	44.38 ± 4.78	51.01 ± 8.32	44.47 ± 8.25	0.145†
45 Days	Mean ± SD	55.62 ± 15.19	22.65 ± 4.06	49.39 ± 19.29	46.98 ± 9.14	0.002†
p-value§		0.186	0.001	0.873	0.002	

SD: standard deviation, IQR: interquartile range.
*Kruskal-Wallis test. †One-way analysis of variance. ‡Friedman test. §Paired one-way analysis of variance.
A p-value < 0.05 was considered significant.

dices of the combined treatment group were significantly lower than those of the control, diclofenac and phenyramidol groups ($p = 0.002$ and $p = 0.0001$), but no statistically significant difference was observed between the other groups ($p > 0.05$).

No statistically significant difference was observed between the thirtieth day biomechanical values of the groups ($p = 0.145$). The differences in pathological radiological and biomechanical scores between the groups are shown in Fig. 4. Histopathological images taken 15, 30, 45 days after surgery are shown in Fig. 5.

DISCUSSION

In our study, we investigated the positive and negative effects of diclofenac, an NSAID, and phenyramidol, an analgesic muscle relaxant, on radiological, biomechanical, and histopathological bone union in a standard fracture model in rat femurs. Fracture healing occurs after the interrelated processes of many biochemical and cellular pathways. Many factors positively and negatively affect fracture healing through these processes. Currently, with a better understanding of the pathophysiology of fracture healing, many innovative treatment methods have been used to shorten the fracture healing time and minimize nonunion problems. There are many treatments and physical and

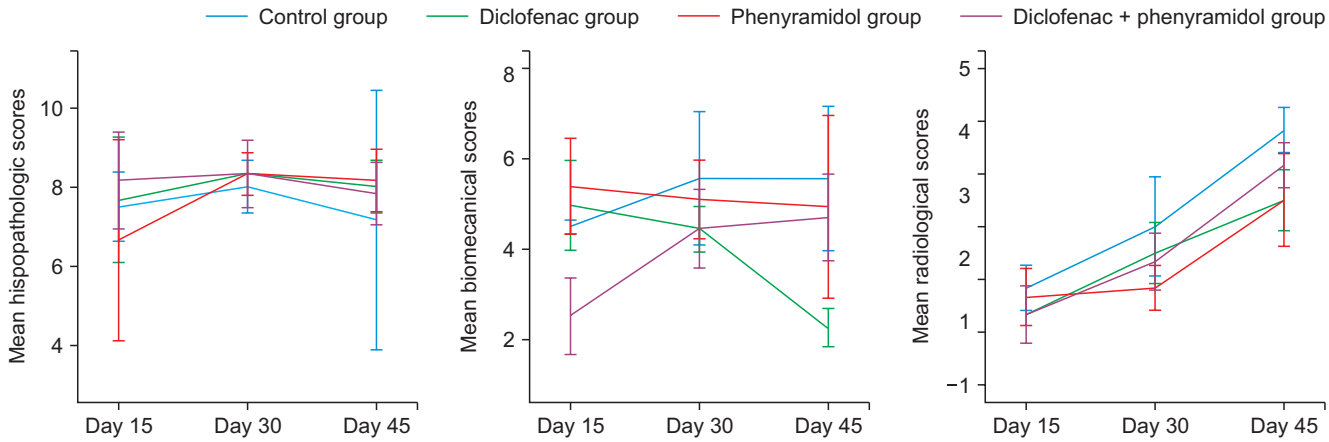

Fig. 4. Pathological, biomechanical, and radiological scores of groups.

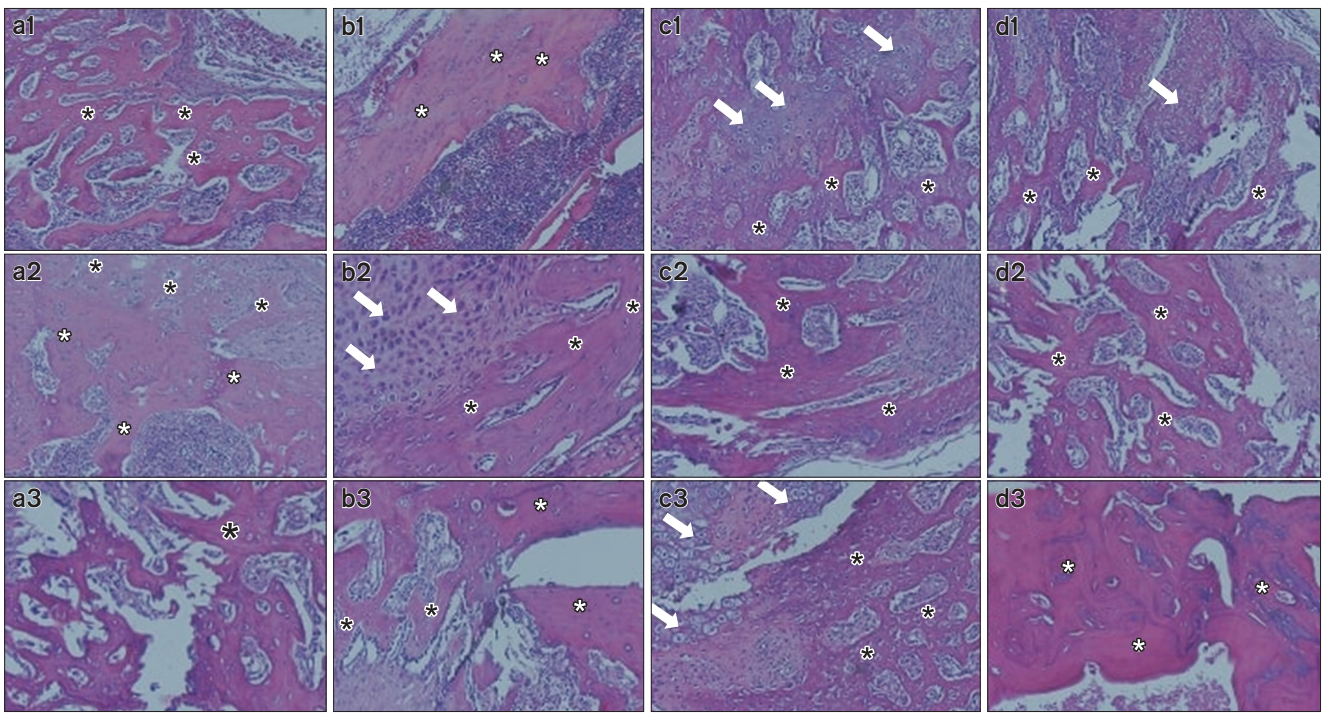

Fig. 5. Histopathological images 15, 30, and 45 days after surgery. a1: Phenyramidol group on day 15 (areas rich in immature bone [black*]). b1: Diclofenac group on day 15 (mature bone tissue [white*]). c1: Phenyramidol + diclofenac group on day 15 (cartilage [arrow] and immature bone tissue [*]). d1: Control group on day 15 (cartilage [arrow] with immature bone tissue [*]). a2: Phenyramidol group on the 30th day (immature [black*] and mature [white*] bone tissue). b2: Diclofenac group on day 30 (cartilage [arrow] and immature bone tissue [*]). c2: Fennyramidol + diclofenac group on day 30 (areas rich in immature bone [black*]). d2: Control group on day 30 (areas rich in immature bone [black *]). a3: Phenyramidol group on day 45 (areas rich in immature bone). b3: Diclofenac group on day 45 (immature [black*] and mature [white*] bone tissue). c3: Phenyramidol + diclofenac group on day 45 (cartilage [arrow] and immature bone tissue [*]). d3: Control group on day 45 (mature bone tissue [white*]). H&E, ×40.

biological therapy methods that affect different steps of this process.[10]

Many factors affecting the fracture healing process have been defined. The type of trauma, fracture treatment option, fixation type, and systemic problems are included. These reasons have been examined and analyzed in many studies. In studies on fracture healing, different animals, such as mice, rats, rabbits, and dogs, were generally used.[11,12]

In a study on fracture healing, different fracture

models, such as closed simple fracture and open osteotomy models, can be created.[13] The fracture, bone defect, and segmentary fracture models can be used. The shape of the fracture and the conditions at the fracture line are very effective in terms of the variety of cells in the environment, the level of growth factors, cytokines in the environment, and the amount of receptors that are present in the cells. In our study, we created a fracture model in rats by performing diaphyseal transverse osteotomy through the middle 1/3 of the femur with a gigli wire. In this way, the standard fractures we created in rats allowed more consistent comparisons and more consistent evaluations of fracture healing in terms of the quality of the reduction made after osteotomy and fracture configuration. We preferred the open fracture model. Although the closed fracture model has been used in many studies in the literature, it has been stated that the presence of adverse conditions such as delayed union and predisposition to nonunion in fractures created by osteotomy via the open method may be more meaningful for revealing the effectiveness of the factor or method to be examined.[14]

In some studies, it has been reported that some muscle relaxant drugs have anti-inflammatory, analgesic, and anti-edema effects similar to those of NSAIDs. Phenyramidol is one of the most frequently used drugs for this purpose. It is a combined analgesic and muscle relaxant drug,[7,15] In our study, we aimed to use phenyramidol for the treatment of post-fracture pain by utilizing the effect profile of phenyramidol. In addition to its strong analgesic anti-inflammatory effect, we examined the publications in which NSAIDs may have negative effects on fracture healing and examined the question of whether phenyramidol can be an alternative drug to NSAIDs for the treatment of post-fracture pain. Although NSAIDs play an important role in the treatment of fracture-induced pain or comorbidities, discussions about their use after fracture continue.[16]

A study conducted on rats in the literature reported that the use of NSAIDs did not delay fracture healing.[17,18] These findings are similar to our histopathological results. In our study, no significant histopathological difference was observed after phenyramidol or diclofenac treatment. In another study, Bhattacharyya et al.[19] reported radiological results of nonunion in patients with humeral shaft fractures 61–90 days after surgery due to NSAID and opioid drug use. In our study, although there was no histopathological difference, no significant difference was observed in the early period when radiological examinations were performed, while a statistically significant difference was observed in the sixth week. Aliuskevicius et al.[20] reported that resistance to torsional force did not return to normal in groups treated with both indomethacin and ibuprofen at 5–8 days. Weeks later, torsional force resistance did not return to normal in the treated group, in contrast to the control group. In our study, when the results of the sixth week were analyzed biomechanically, we observed that there was a significant decrease in the group receiving NSAID treatment compared to the other groups. From this point of view, the biomechanical weakness of the group receiving only diclofenac compared to the other groups may suggest that we should use NSAIDs less or apply combined treatments during the postoperative period. Here, phenyramidol may be an alternative drug because of its analgesic, anti-inflammatory, and muscle relaxant effects. However, additional studies on this subject are needed.

When NSAIDs are used at controlled analgesic doses, their place as a strong trump card is still maintained among those in the analgesic drug groups for the treatment of post-fracture pain. The lack of a statistically significant difference in the use of phenyramidol, which has similar effect profiles, strengthens our use of this drug as an alternative drug group. In cases such as allergic drug reactions and undesirable side effects of NSAIDs, their use as an alternative drug may be of interest. Alternatively, in patients with severe pain after fracture, phenyramidol may be used in combination with NSAIDs. According to our statistical findings, the fact that the group receiving only diclofenac was biomechanically weaker than the other groups may suggest that we should use NSAIDs less or apply combined treatments during the postoperative period. The fact that the control group was radiologically better than the other groups may suggest that while we provided pain control during the postoperative period after fracture, there were also negative effects on union. These findings show that other drugs should be evaluated for their efficacy in treating pain. This led us to hypothesize that the combined use of both drugs may suppress the negative effects of each other on fracture healing. In our study, the use of diclofenac did not significantly differ from the use of the other agents in the early period radiologically, but it was significantly inferior to the use of the other agents radiologically in terms of the long-term results. However, since we compared 2 different drug groups in our study, we applied drug treatment for equal periods of 2 weeks each in all groups due to the standardization of the study. However, although there was no difference in the early period, there were radiologically significant differences in the long-term results, suggesting that NSAIDs may be effective for fracture healing. Another finding that surprised

us with these statistics was that the radiological data of the group receiving combined treatment were better than those of the group receiving only phenyramidol or only diclofenac.

There may be differences between drugs and treatment periods, and the duration and dose of NSAIDs may also influence the effects of these drugs on bone. From this point of view, when our study is compared with the studies in the literature, it is seen that our study has similar results with some studies but not with others.[18,21,22] Since there is no consensus on this issue, it seems that new studies are needed or new types of analgesics may be needed in the postoperative period instead of these drugs.

According to the results of the study, the use of diclofenac alone or phenyramidol alone for postoperative pain management negatively affects fracture healing radiologically and biomechanically. However, this negative effect was less pronounced in the combined treatment groups. However, histologic examination did not reveal any negative or positive effect of phenyramidol, diclofenac, or phenyramidol + diclofenac on fracture healing. Statistically significant differences were observed between the phenyramidol and diclofenac groups in terms of biomechanical and radiologic properties. In particular, the diclofenac group had significantly lower biomechanical properties.

There are limitations in our study, while some studies in the literature prefer closed fracture model, we preferred open fracture model. Again, in many studies in the literature, adverse conditions such as delayed union and predisposition to nonunion have been reported in patients with open osteotomy. The small sample size used in this study is one of our limitations. In addition, the lack of evaluation of biochemical blood parameters and short-term follow-up are among our limitations.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Al-Ajmi TA, Al-Faryan KH, Al-Kanaan NF, et al. A systematic review and meta-analysis of randomized controlled trials comparing surgical versus conservative treatments for acute undisplaced or minimally-displaced scaphoid fractures. Clin Orthop Surg. 2018;10(1):64-73.
2. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem. 2007;42:3-27.
3. Richards CJ, Graf KW Jr, Mashru RP. The effect of opioids, alcohol, and nonsteroidal anti-inflammatory drugs on fracture union. Orthop Clin North Am. 2017;48(4):433-43.
4. Al-Waeli H, Reboucas AP, Mansour A, Morris M, Tamimi F, Nicolau B. Non-steroidal anti-inflammatory drugs and bone healing in animal models-a systematic review and meta-analysis. Syst Rev. 2021;10(1):201.
5. Malanga G, Wolff E. Evidence-informed management of chronic low back pain with nonsteroidal anti-inflammatory drugs, muscle relaxants, and simple analgesics. Spine J. 2008;8(1):173-84.
6. Carley ME, Chaparro LE, Choiniere M, et al. Pharmacotherapy for the prevention of chronic pain after surgery in adults: an updated systematic review and meta-analysis. Anesthesiology. 2021;135(2):304-25.
7. O'Dell TB. Pharmacology of phenyramidol (IN511) with emphasis on analgesic and muscle-relaxant effects. Ann N Y Acad Sci. 1960;86:191-202.
8. Huo MH, Troiano NW, Pelker RR, Gundberg CM, Friedlaender GE. The influence of ibuprofen on fracture repair: biomechanical, biochemical, histologic, and histomorphometric parameters in rats. J Orthop Res. 1991;9(3):383-90.
9. Lane JM, Sandhu HS. Current approaches to experimental bone grafting. Orthop Clin North Am. 1987;18(2):213-25.
10. Baertl S, Alt V, Rupp M. Surgical enhancement of fracture healing: operative vs. nonoperative treatment. Injury. 2021;52 Suppl 2:S12-7.
11. Hausman MR, Schaffler MB, Majeska RJ. Prevention of fracture healing in rats by an inhibitor of angiogenesis. Bone. 2001;29(6):560-4.
12. Urrutia J, Mardones R, Quezada F. The effect of ketopro-

phen on lumbar spinal fusion healing in a rabbit model: laboratory investigation. J Neurosurg Spine. 2007;7(6):631-6.

13. Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. JAMA. 2017;318(24):2466-82.
14. Jackson RA, McDonald MM, Nurcombe V, Little DG, Cool SM. The use of heparan sulfate to augment fracture repair in a rat fracture model. J Orthop Res. 2006;24(4):636-44.
15. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004;28(2):140-75.
16. Wheatley BM, Nappo KE, Christensen DL, Holman AM, Brooks DI, Potter BK. Effect of NSAIDs on bone healing rates: a meta-analysis. J Am Acad Orthop Surg. 2019;27(7):e330-6.
17. Cappello T, Nuelle JA, Katsantonis N, et al. Ketorolac administration does not delay early fracture healing in a juvenile rat model: a pilot study. J Pediatr Orthop. 2013;33(4):415-21.
18. Barry S. Non-steroidal anti-inflammatory drugs inhibit bone healing: a review. Vet Comp Orthop Traumatol. 2010;23(6):385-92.
19. Bhattacharyya T, Levin R, Vrahas MS, Solomon DH. Nonsteroidal antiinflammatory drugs and nonunion of humeral shaft fractures. Arthritis Rheum. 2005;53(3):364-7.
20. Aliuskevicius M, Ostgaard SE, Hauge EM, Vestergaard P, Rasmussen S. Influence of Ibuprofen on bone healing after Colles' fracture: a randomized controlled clinical trial. J Orthop Res. 2020;38(3):545-54.
21. Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. Basic Clin Pharmacol Toxicol. 2008;102(1):10-4.
22. Huss MK, Felt SA, Pacharinsak C. Influence of pain and analgesia on orthopedic and wound-healing models in rats and mice. Comp Med. 2019;69(6):535-45.