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Analysis of the response of non-steroidal anti-inflammatory drugs in bone repair in patients submitted to osteogenic distraction

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ABSTRACT

Distraction osteogenesis is a systemic procedure that can be performed using an external fixator to promote bone defense and repair in different conditions, such as severe trauma and correction of deformities. The bone healing process involves phases of inflammation, which are necessary for healing. Traumatic injuries trigger the production of cytokines that stimulate the release of prostaglandins, which helps in this healing process. This study aimed to analyze the evolution of patients who were admitted to osteogenic distraction without the use of non-steroidal anti-inflammatory drugs (NSAIDs) and to present studies that address the relationship between the use of these drugs and the delay in bone healing. NSAIDs act by inhibiting isoenzymescyclooxygenases (COX) 1 and 2 and their action on COX 2 leads to a decrease in prostaglandins, quenches the inflammatory process, which consequently interferes with the osteogenesis switch and fracture healing. A prospective randomized study reported that the use of NSAIDs in patients admitted to total arthroplasty after hip fractures evolved in more fractures and complications, demonstrating the possible transition of these medications in bone healing. In this study, osteogenic distraction without the use of non-steroidal anti-inflammatory drugs (NSAIDs) showed good results in bone repair in patients with severe fractures. Patients demonstrated that this treatment provided an efficient process of bone healing and neoformation, which resulted in a shorter duration of the distraction process. It is concluded that the interference of these drugs in the inflammatory response can impair bone healing.

Keywords: Boneregeneration, Distraction, Fastener, Consolidation, Prostaglandins and non-steroidalanti-inflammatorydrugs.

1 INTRODUCTION

Distraction osteogenesis is a surgical procedure that can be performed with the use of an external fixator, which is often used by the medical specialty of orthopedics and aims to promote bone regeneration and repair. This technique refers to the gradual separation of vascularized bone fragments that trigger bone neoformation (NESI, 2001). It is applied in cases such as high-energy trauma with

serious injuries (such as being run over, motor vehicle accidents, falls from great heights), correction of bone deformities, discrepancy in limb length, or resection of malignant tumors (SAIHAN, 1992).

Bone repair is a response of the body to restore bone continuity, without increasing the volume of bone cells (TAY et al., 1998). On the other hand, bone regeneration is a natural process of the body that leads to the differentiation of osteoprogenitor cells that give rise to osteoblasts, resulting in the formation of new bone and an increase in the volume of bone cells (AL-AQL et al., 2008). This organic mechanism can be stimulated by surgical intervention such as distraction osteogenesis (TAY et al., 1998).

The bone healing process involves two phases, primary bone healing, in which the course of inflammation occurs, and secondary bone healing, in which bone callus formation occurs. In addition, the secondary phase is subdivided into three phases: inflammatory, reparative and remodeling (DUTTON, 2012). One of the most important molecular signals to initiate these steps after an injury is the release of pro-inflammatory cytokines that stimulate angiogenesis and increase extracellular matrix synthesis (SFEIR et al. 2005).

Cytokines act in conjunction with growth factors by stimulating the release of prostaglandins (PGs) by osteoblasts, which have important functions for fracture healing and trigger the differentiation of mesenchymal stem cells (MSCs) into chondrogenic and osteogenic cells (EINHORN; GERSTENFELD, 2014). These PGs are stimulated by isoenzymescyclooxygenases (COX) 1 and 2, mainly COX 2 involved in the inflammatory response (CHEN, DRAGOO, 2013).

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes, which are responsible for the hydrolysis of arachidonic acid into prostaglandins (PGs) and thromboxanes (TXA-2), promoting a decrease in the inflammatory process and, consequently, in pain (PANCOTE, 2009). However, the suppression of inflammation caused by this drug can negatively affect the mechanisms of osteogenesis and fracture healing (CHIAKAZUet al., 2007). Therefore, these drugs should be administered in immediate postoperative treatments for short periods (RIBEIRO et al., 2007).

In this context, our study aimed to analyze the evolution of patients who underwent distraction osteogenesis without the use of non-steroidal anti-inflammatory drugs (NSAIDs) and to present studies that address the relationship between the use of these drugs and delayed bone healing.

2 METHODOLOGY

This study consists of a case series with descriptive, quantitative, and qualitative analysis of the medical records of patients undergoing surgical treatment of distraction osteogenesis, without the use of non-steroidal anti-inflammatory drugs (NSAIDs) during the bone regeneration phase.

The medical records of six patients living in Maringá, Paraná, who underwent the surgical procedure between 2017 and 2023 were reviewed. The descriptive analysis was performed based on

imaging studies to evaluate the evolution of bone healing, ranging from bone neoformation to effective consolidation.

The patients included in the study underwent surgical treatment with an external fixator for lengthening, transport, and correction of bone deformities resulting from trauma. The surgical procedure performed stimulates bone neoformation through distraction osteogenesis. Importantly, these patients did not use NSAIDs during the bone regeneration phase.

The inclusion criteria were the patients' acceptance to participate in the study, through the signing of the Free and Informed Consent Form (ICF). Smokers, alcoholics, and individuals with comorbidities such as hypertension, osteoporosis, and diabetes mellitus were excluded from the study.

Relevant studies on the subject, from databases such as Scielo, Pubmed, LILACS, Google Scholar and CAPES Journal, were used to support the research.

The intervention procedures of this study were submitted to and approved by the Research Ethics Committee of UNICESUMAR, CAEE No. 66.710.423.0.0000.5539, opinion number 5.590.121, according to resolution No. 466/2012. All research participants signed the Free and Informed Consent Form (ICF) in two copies of the same content and form, and were given one copy. The collected data were analyzed on the *Google Forms* platform and later tabulated in *Microsoft Office Excel® 2013*, for data interpretation simple descriptive statistics were used.

3 RESULTS

This study analyzed a case series of patients undergoing the distraction osteogenic procedure to evaluate bone repair in individuals who did not receive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) during the regeneration phase, when distraction osteogenesis occurs until effective union.

The patients analyzed in this section were in the age group of 23 to 27 years and underwent an osteogenic distraction procedure, ranging from 4 to 12 cm, during a treatment period of 8 to 12 months. It is important to note that all patients did not have risk factors, such as alcoholism and smoking, and also did not have comorbidities such as hypertension, diabetes mellitus and osteoporosis. However, severe fractures and complications prior to distraction, such as osteomyelitis, pseudarthrosis, and bone deformities, were identified.

The table (below) presents relevant information to evaluate the results of each patient's X-ray examinations.

Table 1 - Presents information on patients undergoing distraction osteogenesis, including gender, age, type of fracture, and presence of complications prior to the procedure. Patients were predominantly male, ranging in age from 23 to 27 years.

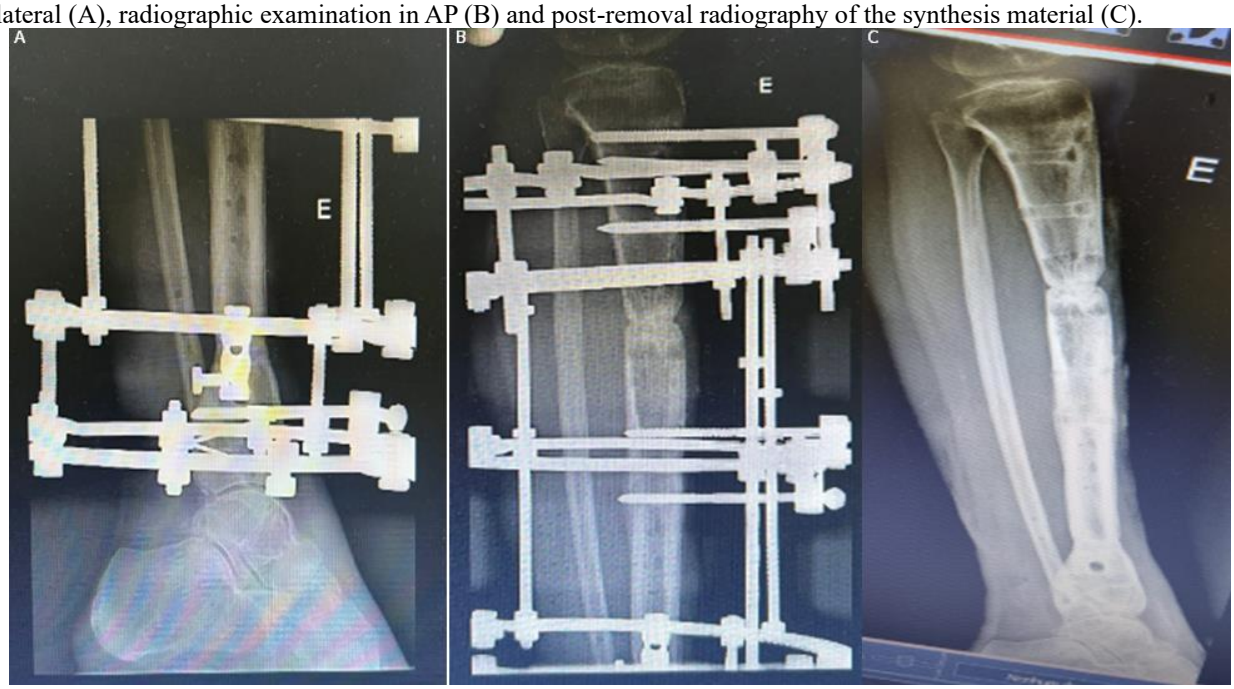
PATIENTS	GENDER	AGE	FRATURE TYPE	PREVIOUS COMPLICATIONS
Patient 1	♀	26	Open fracture of left tibia and fibula	Osteomyelitis
Patient 2	♂	27	Comminuted fracture of the diaphysis of the right femur	
Patient 3	♂	26	Open fracture in the right distal femur	
Patient 4	♂	23	Closed and comminuted fracture of the diaphysis of the left femur	Osteomyelitis and thrombosis
Patient 5	♂	26	Open fracture of the right forearm	Osteomyelitis
Patient 6	♂	24	Fracture of left femur	Osteomyelitis and pseudoarthrosis

Source: Prepared by the authors based on the results of the research (2023).

In the case of **patient 1**, it is a 26-year-old woman who suffered a high-energy accident involving a motorcycle and a car. The accident resulted in an open fracture of the left tibia and fibula. A temporary fixation of the fracture was performed with an external fixator tube by tube (07/12/21) soon after, for definitive fixation, plates and screws were placed. During the evolution of the case, the patient developed osteomyelitis, which led to the conversion of the surgery to bone resection and transport (distraction osteogenesis) with the use of the Ilizarov fixator (04/26/22) and suspension of the use of NSAIDs during the bone regeneration phase.

Over a period of approximately 12 months, a distraction of approximately 5 cm was performed, evidencing a continuous progress in bone consolidation and neoformation, indicating an effective healing process, which resulted in the removal of the fixator (Image 1).

Image 1 - Signs of bone healing in the final phase of distraction osteogenesis. Radiographic examination of the leg bones in lateral (A), radiographic examination in AP (B) and post-removal radiography of the synthesis material (C).



Source: Personal collection (2023).

In the case of **patient 2**, a 27-year-old man, he was involved in a high-energy accident involving two motorcycles. The accident resulted in a comminuted fracture of the shaft of the right femur. A surgical procedure was performed with the use of a tube-by-tube external fixator (11/17/19) as temporary fixation. On 11/22/19, a bone resection was performed to start the bone transport process, using an intramedullary nail in conjunction with a linear external fixator (LRS - Limb Reconstruction System). This stage of treatment lasted approximately 8 months. On 07/17/20, at the end of the bone distraction, the expected goal of 6 cm was achieved. At this point, the synthesis materials were removed, ending the treatment.

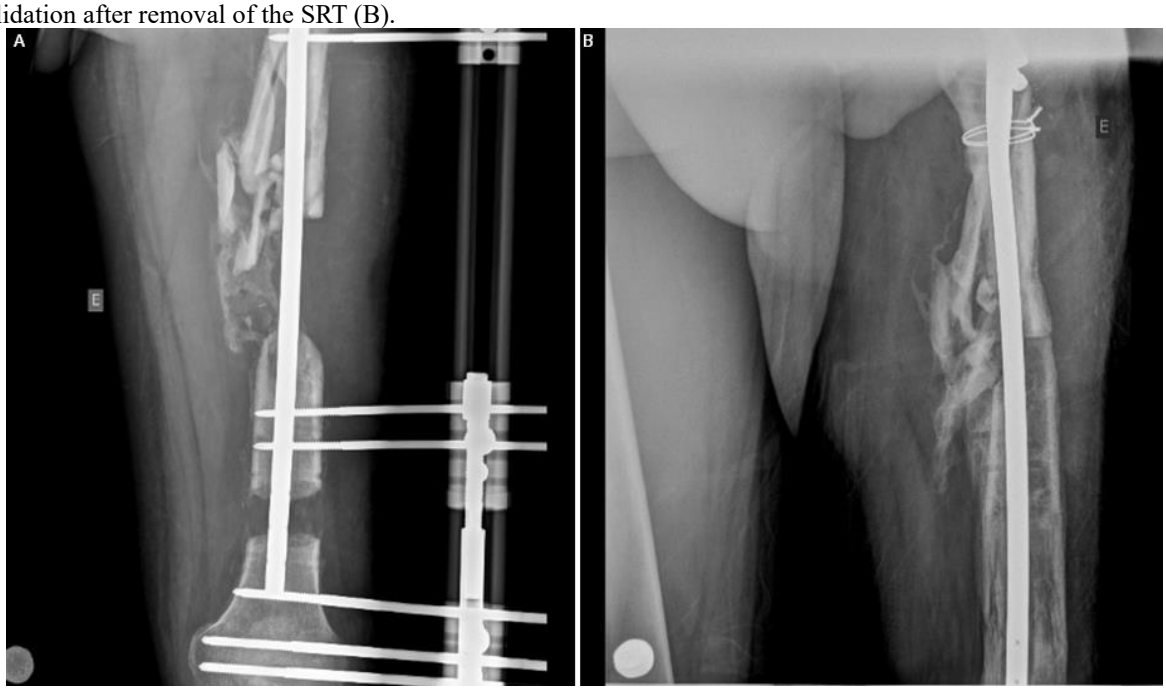
In the case of **patient 3**, a 26-year-old man, he was involved in a high-energy accident involving a motorcycle and a motor vehicle. As a result, he suffered an open fracture to his right distal femur. A surgical procedure was performed with the use of a tube-by-tube external fixator (10/18/18) for temporary fixation. Subsequently, (10/26/18), bone resection was performed and the Ilizarov fixator was placed to start bone transport.

During a period of approximately 10 months of bone distraction, the patient showed progressive improvement, with evidence of bone healing and formation of new tissue, indicating a positive response to treatment. In total, a bone transport of 5 cm was achieved. Subsequently, the patient underwent an Ilizarov fixator removal procedure on 12/13/19.

In the case of **patient 4**, a 23-year-old man, he suffered a motorcycle fall that resulted in a closed and comminuted fracture in the diaphysis of the left femur. He underwent placement of a proximal femoral nail (PFN) (06/22/19). During the course of the course, the patient developed thrombosis and osteomyelitis, requiring the placement of bone cement with antibiotics in the focus of infection (07/26/19). However, there was progression of osteomyelitis, requiring resection of the bone fragment and placement of a linear external fixator (LRS - Limb Reconstruction System) to start distraction osteogenesis on the nail on 09/15/19 (Image 2).

During a period of approximately eight months of distraction osteogenesis, notable signs of bone regeneration were observed, indicating a positive response to the procedure performed. There was a total of eight cm of bone transport to the distal fragment, and the SRN was removed on 05/29/20 (Image 2).

Image 2 - Resection of the affected bone fragment and placement of a linear external fixator (LRS) (A) and Signs of bone consolidation after removal of the SRT (B).



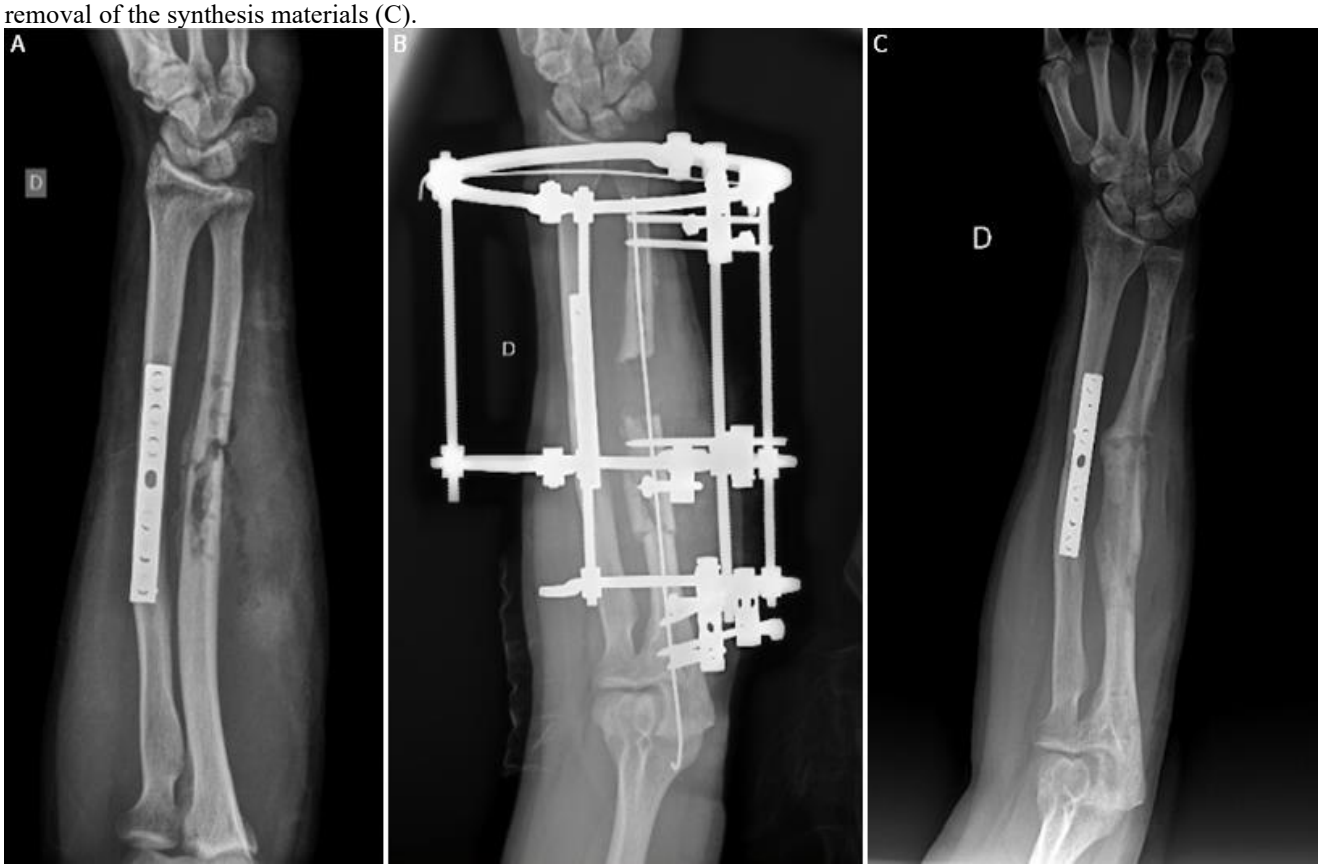
Source: Personal collection (2023).

In the case **of patient 5**, a 26-year-old man, he suffered a fall of the same level while playing sports, resulting in an open fracture of the right forearm. On 11/08/21, a plate and screws were placed to fix the fracture. During the recovery process, the patient developed a bone infection, known as osteomyelitis (Image 3), which led to the removal of the fixation material and the resection of the infectious focus on 02/14/22.

Then, on 03/22/22, a procedure called Masquelet was performed, which consists of two steps: in the first stage, a spacer containing bone cement and antibiotics was inserted, and in the second stage, the space created was filled with bone graft taken from the iliac bone. However, there was a recurrence of the infection, which required the removal of the fixation material and the graft, and the beginning of the bone transport procedure using the Ilizarov method and insertion of an intramedullary Kirschner wire as a guide on 05/03/22 (Image 3)

During the follow-up period, which lasted about 8 months of bone transport, the patient showed progressive improvement, with visible evidence of bone healing and formation of new tissue, indicating a positive response to treatment. In total, 4 cm osteogenic distraction was performed. The Ilizarov fixator was removed on 01/30/23, followed by the removal of the wires on 02/03/23 (Image 3).

Image 3 - Evolution of the fracture in 3 months with signs of pseudarthrosis and osteomyelitis (A), placement of the ilizarov circular external fixator and intramedullary Kirschner wire for bone transport (B) and signs of bone consolidation after removal of the synthesis materials (C).



Source: Personal collection (2023).

In the case **of patient 6**, a 24-year-old man, he suffered a high-energy trauma in a motorcycle accident with a motor vehicle, resulting in a fracture of the left femur due to the high impact. The fracture was treated (11/19/15) by placing an intramedullary nail. During the treatment process, the patient developed osteomyelitis (bone infection) and pseudarthrosis (lack of bone healing), leading to the removal of the synthesis material and the application of an Ilizarov circular external fixator to assist in the compression of the fracture focus on 08/07/17. However, due to the persistence of osteomyelitis, it was necessary to resect the infectious focus and start the bone transport process on 04/20/18.

During the follow-up period, which lasted about 12 months of distraction osteogenesis, signs of bone union were observed, resulting in a total of 12 cm of distraction osteogenesis. This evolution culminated in the removal of the fixative on 04/26/19.

4 DISCUSSION

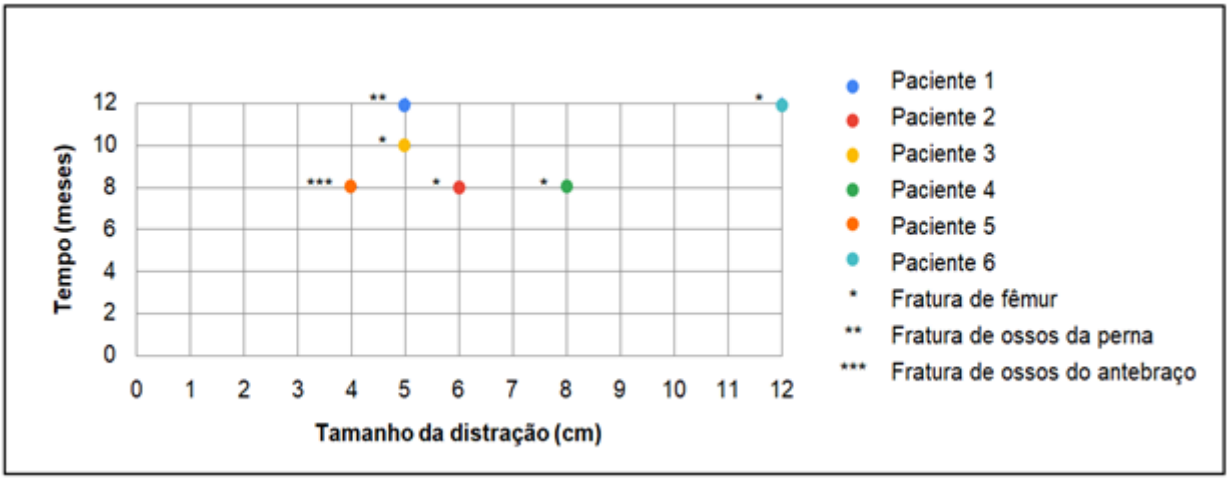
The results of the radiographs confirm the general findings of the study, demonstrating that distraction osteogenesis promoted bone regeneration with bone length gain. In addition, efficient consolidation was observed, even in patients with severe fractures and previous complications. X-rays play a key role in providing a detailed view of the evolution of the healing process in each patient.

These tests reinforce the importance of excluding non-steroidal anti-inflammatory drugs (NSAIDs) during the bone regeneration phase, as this approach seems to have contributed significantly to obtaining more favorable results, reflected in the reduction of the time required for the distraction process and in the reduction of complications, such as pseudarthrosis and additional fractures. The exclusion of NSAIDs may have played a significant role in improving patients' clinical outcomes.

In a prospective randomized study, a total arthroplasty was conducted in patients who underwent the surgical procedure of total arthroplasty after hip fractures, with the aim of preventing bone formation in abnormal sites, such as muscles, for example, (heterotopic ossification). This sample of patients was divided into two groups: one group that received NSAIDs and the other control group without this treatment. The study showed efficacy in reducing the risk of abnormal ossification, but the treated group had more additional long bone fractures and complications, such as pseudarthrosis (bone nonunion) and the result brought statistically significant values reporting that these anti-inflammatory drugs are harmful to fracture healing (BURD, et al., 2003).

The graph below illustrates the relationship between the required distraction time and the size of the distraction achieved in each patient.

Graph 1 - Relationship between time and size of distraction osteogenesis



Each point on the graph represents a specific patient. The horizontal axis represents the size of the distraction in centimeters, while the vertical axis represents the distraction time in months. To identify the limb affected by the fracture, asterisk symbols (*) are used. One asterisk indicates femur fracture, two asterisks indicate fracture of leg bones, and three asterisks indicate fracture of forearm bones. This visual representation makes it possible to observe the variation in distraction time in relation to the size of the distraction in different patients, as well as to identify the association with the affected limb.
Source: Prepared by the authors based on the results of the research (2023).

It is relevant to highlight that patients 1, 4, 5 and 6 faced complications prior to distraction osteogenesis, such as the occurrence of osteomyelitis. In addition, patient 4 also had thrombosis, while patient 6 manifested pseudarthrosis before the procedure. These complications may have had a significant influence on the timing and size of the bone distraction in each of these cases. In addition, we observed (graph above) that patients exhibit different combinations of distraction time and size,

suggesting that other individual factors may influence these results. The presence of previous complications, such as osteomyelitis and thrombosis, may also have impacted the timing and size of distraction in some patients.

Osteomyelitis is a common complication that can have a significant effect on bone healing by slowing the healing process (BLICK, 1986). This condition is an inflammatory process caused by infection that affects the bone and its bone marrow. There are two main forms of osteomyelitis: acute and chronic. The acute form manifests early with gradual and localized pain over several days, accompanied by tenderness, warmth, erythema, swelling, and systemic symptoms such as fever and chills. On the other hand, the chronic form may have few symptoms or obvious signs, with a later presentation, including pain, erythema, or edema (OKIKE, 2006). These considerations emphasize the complexity and individuality of the bone healing process in patients undergoing distraction osteogenesis.

Although the study did not specifically evaluate the effect of NSAIDs in these patients, it is important to consider the influence of these drugs on the bone healing process.

Previous studies (Chiakazu et al., 2007) have suggested that NSAIDs may negatively affect the mechanisms of osteogenesis and fracture healing, as the bone regeneration process involves several steps, including the inflammatory response, bone callus formation, and bone remodeling. During these steps, cytokines and prostaglandins released by COX-1 and COX-2 enzymes play a key role. NSAIDs, by inhibiting these enzymes, can reduce inflammation and pain, but there is evidence that this suppression may negatively affect bone healing.

These findings provide preliminary evidence that NSAIDs exclusion may be a beneficial approach to bone repair and regeneration in patients undergoing distraction osteogenesis. This information can contribute to a better understanding of the factors that influence the bone healing process and to the identification of therapeutic strategies. Future investigations with larger samples and control groups may provide more robust evidence and corroborate the importance of not using NSAIDs for a long time in these patients.

5 CONCLUSION

Based on the analysis of the cases, it is possible to conclude that the distraction approach of osteogenesis without the use of non-steroidal anti-inflammatory drugs (NSAIDs) presented favorable results in bone repair and regeneration in patients with severe fractures and associated complications. Patients undergoing this treatment showed an efficient process of bone healing and neoformation, which resulted in a shorter duration of the distraction process.

Throughout the bone healing process, one of the critical steps is the inflammatory response, the interference of which can negatively affect bone healing. The study demonstrated that the absence of

NSAIDs during the bone regeneration phase contributed to the positive results observed. The use of these drugs can inhibit the inflammatory response, thus affecting the efficiency of bone healing. It has been found based on previous studies that NSAIDs can affect osteogenesis by inhibiting COX enzymes, which are responsible for prostaglandin production.

However, it is important to highlight some limitations of this study. First, the sample size was relatively small, which may limit the representativeness of the results. In addition, the absence of a control group with NSAIDs made it impossible to directly compare the effects of not using these drugs. In addition, the lack of long-term follow-up of patients also represents a limitation, since it made it impossible to perform a comprehensive analysis of possible late complications.

Therefore, future research with larger samples, control groups, and extended follow-up is needed to confirm and expand the findings of this study. These further investigations may have relevant clinical implications in orthopedics, providing a direction for more appropriate and optimized practices to promote bone healing in patients undergoing this type of surgical treatment.

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