Journal of Kerbala for Agricultural Sciences Issue (4), Volume (10), (2023)

Evaluation bone healing agents: radiological presentative on lidocaine and diclofenac in rabbits

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https://doi.org/10.59658/jkas.v10i4.1309

Received:

Nov. 05, 2023

Accepted:

Dec. 11, 2023

Published:

Dec. 15, 2023

Abstract

This study aimed to assess the impact of intraosseous injections of 2% lidocaine hydrochloride and 3.75% Diclofenac on bone regeneration. Forty-five adult male rabbits of a local breed were used to create a 3.5mm hole in the proximal third of the medial aspect of the tibia using an electric drill, with continuous isotonic regular saline irrigation to prevent thermal necrosis. The rabbits were randomly divided into three groups of fifteen each (n=15): a control group without any treatment, Group 1 (Lidocaine HCl), which received a daily dose of 2% lidocaine HCl (2 mg/kg body weight) for five days post-operation (P.O.), and Group 2 (Diclofenac), which received 3.75% Diclofenac (20 mg/kg body weight). Radiographic evaluations were conducted at the end of the 7th, 14th, and 21st days P.O. The findings demonstrated accelerated bone regeneration and development in Group 1 compared to Group 2 and the control group. In conclusion, intraosseous injection of 2% Lidocaine HCl (2mg/kg B.W.) showed a stimulatory effect on bone healing, with osteogenic tissue and trabecular bone formation being visible in radiographic images at the end of the first week, indicating a more effective outcome compared to the Diclofenac and control groups.

Keywords: Lidocaine hydrochloride, diclofenac, bone healing, rabbit model, radiological analysis, comparative study, intraosseous

Introduction

Bone healing is a crucial process in the field of medical and surgical sciences, with various factors playing significant roles in either promoting or inhibiting this process. There is an increasing interest in medical research regarding the impact of certain substances on bone healing, including the use of lidocaine and diclofenac. These substances have diverse applications and effects on bone healing and tissue regeneration in general, the potent and rapid action of anesthetics, significant in clinical use, has allowed for safe, complex surgeries [1] and, with the advancement in anesthesia techniques, a variety of procedures are now feasible under local anesthesia.[2,3]

Local anesthesia means the loss of pain in a specific limited area [4], briefly blocking pain signals in nerve fibers by blocking sodium channels on nerve cells, reducing action potentials and preventing signal transmission [5], halting pain transmission to the brain

[6,7]. Which is important to decrease the cost and side effects of general anesthesia, especially in large animal species. This depends on the local anaesthetic agents' ability to cross nerve sheaths and neural membranes [8]. However, with the ever-increasing awareness of pain management that could be used in all veterinary species with a safety dose especially in dogs and rabbits.[9,10]

Lidocaine hydrochloride, in various forms and concentrations, is widely utilized in veterinary medicine [11,12]. Its versatility extends to applications beyond pain management, encompassing its potential influence on tissue regeneration processes, including bone healing. Besides its established use for intraosseous (IO) injections and its capacity to regulate blood pressure and cardiac rhythm [13] and its mainly excreted in the urine, with 90% as metabolites and 10% as the unchanged drug [14], also, its rapid onset, strong effectiveness, and low allergy risk [13]. lidocaine's role in veterinary surgery is notable for its rapid onset, ease of administration, and facilitating smooth postoperative recovery [15]. Lidocaine, a local anaesthetic, blocks nerve impulses by inhibiting sodium ion influx into nerve cells, resulting in a reversible loss of sensation [16]. Combining drugs with lidocaine extends postoperative analgesia duration, achieving rapid sensory and motor block with minimal pain scores [17]. This broad utility extends across a spectrum of procedures and administration routes [18]. Underscores its significance in the context of tissue healing and regeneration, including its impact on bone tissue healing.

Diclofenac, a widely used non-steroidal anti-inflammatory drug (NSAID), has potent analgesic and anti-inflammatory properties [19]. Globally, injury and bone fracture patients often receive NSAID treatment. These drugs are effective in post-traumatic therapy due to their combined anti-inflammatory action and potent analgesic effects. However, it's worth noting that some in vitro studies have suggested that NSAIDs, including diclofenac, may hinder bone fracture healing or the fixation of hydroxyapatite-coated implants [20,21]. Diclofenac, in particular has been implicated in negatively impacting bone healing [22], The impact of these drugs on bone formation is linked to reduced remodeling and calcification, diminished blood flow, and altered inflammatory response at fracture sites [23,24]. Furthermore, on a cellular level, diclofenac may have adverse effect on pre-osteoblast cell growth.[25,26]

Diclofenac is used for various medical condition [27] and possesses abroad spectrum of anti-inflammatory and analgesic properties [28,29]. However, its use is associated with gastric damage, a potential side effect of NSAID use.[30,31]

Numerous studies have been published regarding the cytotoxic effect of local anaesthetics on virous cell types, including osteoblastic cell like [32]. Additionally, IO injection, which involves the direct administration of anaesthetic agent into the bone, is experiencing a resurgence in popularity for regional anaesthesia [33]. there are numerous injection methods available for local anaesthesia, with intraosseous injection being one of the historical techniques used since the early 1900s. despite the advent of plastic catheter, which facilitated easier intravenous access and become the preferred choice for many medical practitioners, intraosseous injection remains a valuable technique,

especially in dentistry and surgical procedures requiring significant amount of anaesthetic agent [34, 35].

Materials and Methods

Animals and Experimental Design

In this study, 45 adult male rabbits of a local breed were utilized, and they underwent a one-week acclimation period in dedicated cages before the experiment commenced .[36]. These rabbits were chosen as a suitable model for bone healing research due to their relatively fast bone turnover and similarity to human bone physiology.

The rabbits were divided into three experimental groups as follows:

Control Group: fifteen rabbits in this group did not receive any drug intervention and were the control group to assess natural bone healing.

Group 1: Another fifteen rabbits received intraosseous injections of Lidocaine at a dose of 2 mg/kg B.W. once daily for five days, following the protocol by.[37]

Group 2: The final group consisted of fifteen rabbits that underwent intraosseous injections of Diclofenac at a dose of 20 mg/kg B.W. once daily for five days, as [38] outlined.

The study was conducted over 21 days, allowing for comprehensive observation of the bone healing process throughout the experiment.

Surgical procedure

Preoperative preparation

Prepare the proximal third of the medial aspect of Tibia, by clipping and shaving the hair, clean the area by tap water and medical soap, then disinfect the surgical site with 70% ethyl alcohol. after induction of general anesthesia and put the animal in lateral recompact and the medial aspect of the hind limb expose the surgeon, cover all the body with sterile drapes except the surgical site.

Anesthetics protocol

Given the challenges associated with anesthetizing rabbits [39], induction of general anesthesia was achieved through an intramuscular injection of 2% xylazine hydrochloride at a dose of 17.5 mg/kg body weight, followed by a re-injection of 10% ketamine hydrochloride at 25 mg/kg body weight after 10 minutes.[40]

Surgical technique (Figure 1)

Create 2cm length skin incision by sharply dissect at the proximal and medial aspect of Tibia, separate all the soft tissue ,then remove the periosteum induced 3.5 mm hole defect with electrical drill with dropping normal sterile isotonic solution to prevent thermal necrosis of the bone [41],reposition the soft tissues and close the skin by simple interrupted suture pattern using 2/0 suture materials .the experimental animals divided to 4 groups as mentioned in the experimental design before,

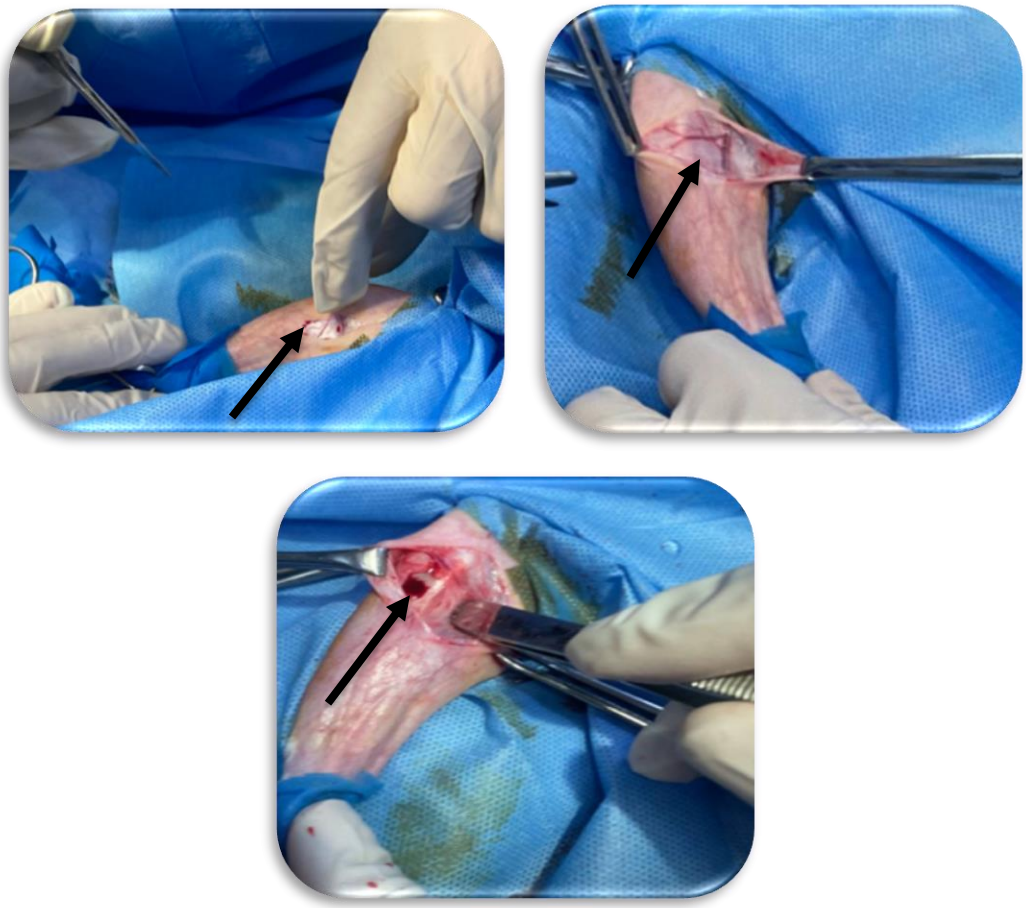

Figure (1): The surgical stages,1. Skin incision,2. Expose the medial aspect of the proximal end of the Tibia,3. Induce a 3.5 mm hole.

Postoperative car

1. The site of operation was daily checked.
2.Daily systemic antibiotics injection for three days. Penicillin and streptomycin 10 Iu/Kg. B. W. and 5mg/Kg. B. W. respectively
3.Remove the suture materials seven days

Ethical statement

Before starting this study, the local animal care committee granted ethical approval and use at the College of Veterinary Medicine, University of Baghdad (number P.G 2035 on 25/9/2023).

Results and Discussion

Histopathological results

First week

Control Group: The radiographs showed well-defined borders of the induced hole with slight new fibrous tissue formation inside the bone defect Figure 2.

Group 1: The radiographs showed more radiopaque new tissue formation than the control group. Figure 3.

Group 2: The radiographs revealed a radiolucent area, indicating minimal soft tissue formation inside the hole. Figure 4

Second week

1.Control Group: Radiographs showed a well-defined border of the induced hole, the little periosteal reaction of the adjacent bone towards the bone defect, and a radiolucent area inside the hole. Figure 5

2.Group 1: Exhibited a clear, high sclerotic area at the hole border with a radiopaque area inside the bone defect. Compared to the other treatment group, the specifics for this group needed to be more detailed. Figure 6

3.Group 2: The radiographic findings included a clear and well-defined border of the induced hole, little soft tissue formation inside the bone defect, and a slight periosteal reaction around the hole border Figure 7.

Third week

1.Control Group: The radiographic image showed a prominent and well-defined induced hole defect surrounded by a high sclerotic area. The inside of the hole remained a radiolucent area, indicating no conversion to complex tissue formation. Figure 8.

2.Lidocaine 2 mg Group: Most of the bone defect in the hole appeared to have disappeared and converted to hard tissue, with a high sclerotic area around the border of the induced hole defect. The exact comparison between this and the other treatment groups must be specified. Figure 9

3.Diclofenac Group: The radiographic image showed a homogenous high-density area around the induced hole defect, but a radiolucent area was still inside the bone defect. Figure 10

Lidocaine, a local anaesthetic, has complex effects on tissue healing [42] There are different references refer to the effect of lidocaine in which our results agree with [43] who found that Lidocaine's potential positive effect on bone healing, as indicated by our results, could be attributed to its analgesic and anti-inflammatory properties. By reducing pain and inflammation, lidocaine might create a more conducive environment for bone regeneration. While these results disagree with [44], who suggest that lidocaine may have an inhibitory effect on bone regeneration in vitro study.

The radiographic findings suggest that lidocaine, particularly at higher doses, facilitates more efficient bone healing compared to diclofenac. This might be due to lidocaine's ability to mitigate pain without significantly impeding the healing process, unlike diclofenac, which might inhibit critical aspects of bone regeneration.[43] .

Diclofenac, a non-steroidal anti-inflammatory drug (NSAID), is known to delay fracture healing. This is mainly due to its effect on osteoblasts, the cells responsible for new bone formation. NSAIDs like diclofenac can impair the proliferation and activity of osteoblasts, particularly in the early stages of bone healing [45]. Diclofenac use leads to delayed bone healing by reducing osteoblast activity [46,47,48]. This supports concerns about NSAIDs, like Diclofenac, inhibiting bone healing, especially when COX-2 is suppressed [49,50,51,52]. Its anti-inflammatory effects may hinder necessary inflammation for bone repair, questioning NSAID use in optimal bone regeneration.

Additionally, NSAIDs impact prostaglandin synthesis by inhibiting COX-1 and COX-2 [53], negatively affecting bone healing[54]

1.Lidocaine's Role in Bone Healing: Despite its primary use as a local anesthetic, Lidocaine does not significantly impair bone healing. This was evidenced by the more advanced bone healing observed in the Lidocaine group compared to the Diclofenac group.

2.Diclofenac's Inhibitory Effects: Diclofenac, a typical NSAID, apparently inhibits bone healing. Its use, especially systemically, should be cautiously approached in contexts where bone healing is a priority.

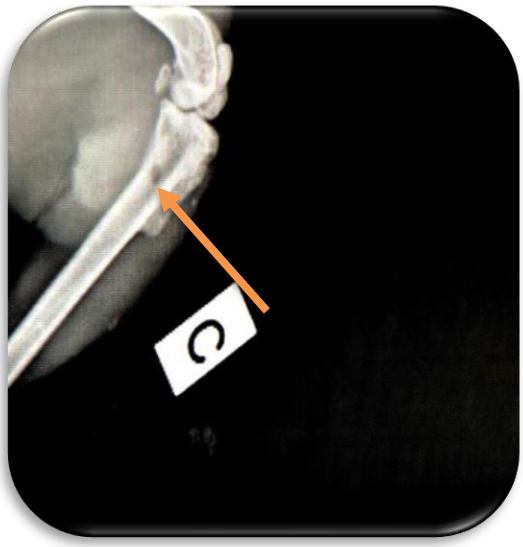

Figure (2): Radiographic image of tibial bone at the end of 1st -week post-operation, control group showing an apparent bone defect with signs of early healing.

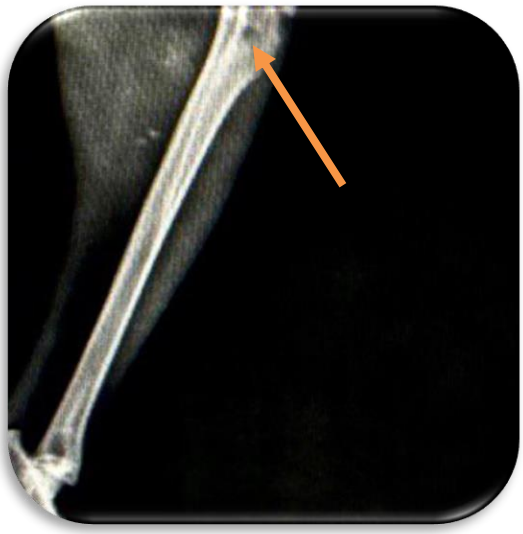

Figure (3): Radiographic image of tibial bone at the end of 1st -week post-operation, lidocaine 2 mg/kg B.W. group showing enhanced radiopaque new tissue formation.

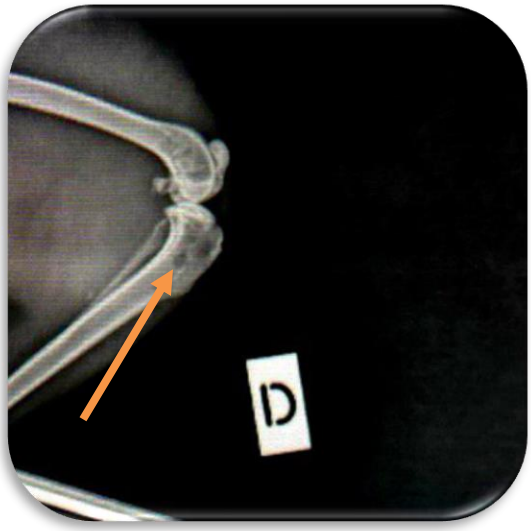

Figure (4): Radiographic image of tibial bone at the end of 1st-week post-operation, diclofenac group showing a radiolucent area with minimal soft tissue formation.

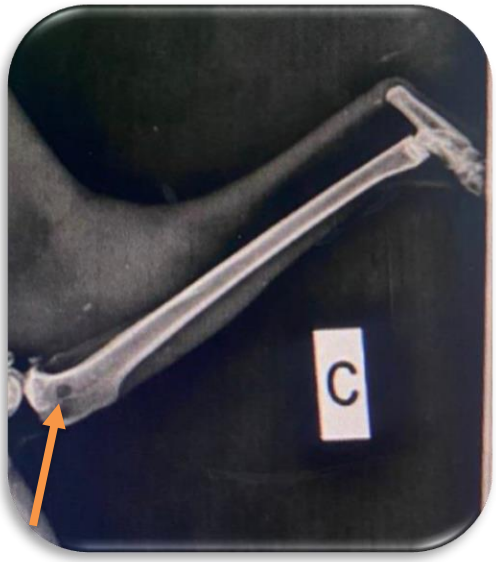

Figure (5): Radiographic image of tibial bone at the end of 2nd -week post-operation, control group showing a clear border of the hole, slight periosteal reaction near the defect, and a radiolucent area within

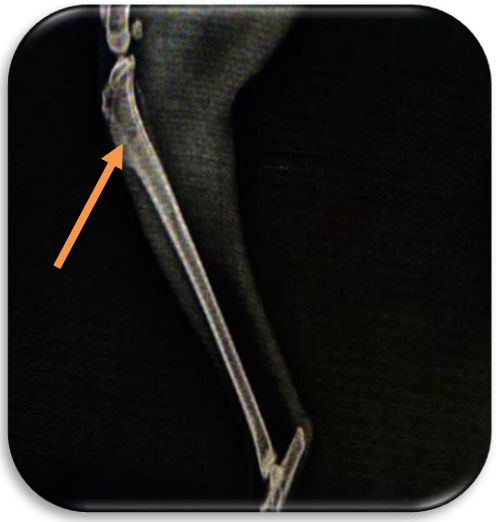

Figure (6): Radiographic image of tibial bone at the end of 2nd -week post-operation, lidocaine 2 mg/kg B.W. group showing a highly sclerotic, clear border around the bone defect with a radiopaque area inside

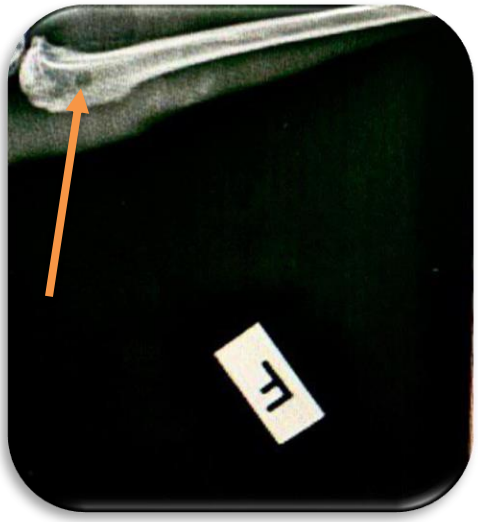

Figure (7): Radiographic image of tibial bone at the end of 2nd-week post-operation, diclofenac group showing well-defined hole border, minimal soft tissue in the defect, and slight periosteal reaction around the hole.

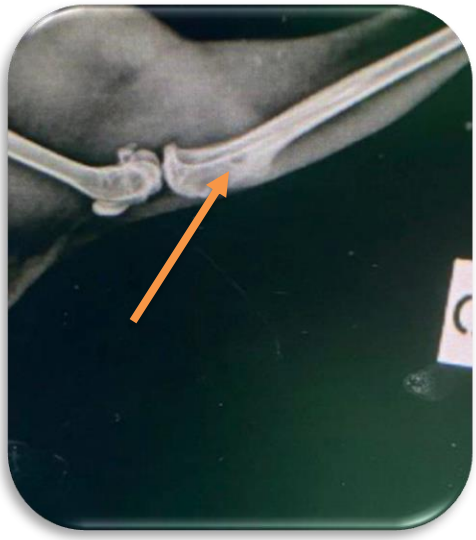

Figure (8): Radiographic image of tibial bone at the end of 3rd.-week post-operation, control group showing well-defined hole defect, high sclerosis around it, and a radiolucent center indicating no complex tissue formation.

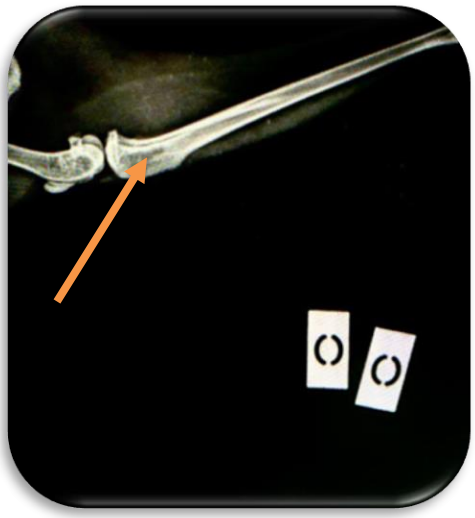

Figure (9): Radiographic image of tibial bone at the end of 3rd. -week post-operation, lidocaine 2 mg/kg B.W. group showing significant hard tissue conversion in the bone defect, with pronounced sclerosis around the hole's border.

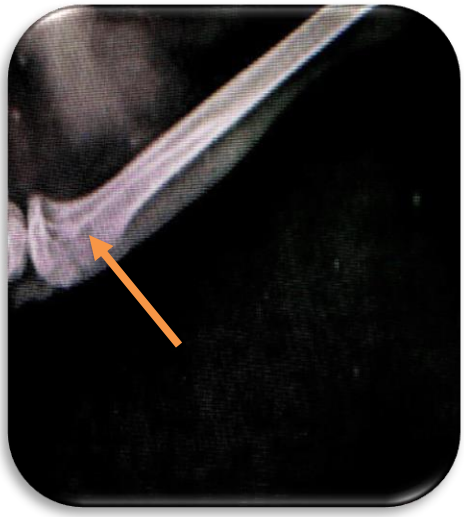

Figure (10): Radiographic image of tibial bone at the end of 3rd. -week post-operation, diclofenac group showed a homogeneous high-density area around the hole defect, with a persistent radiolucent area inside the bone defect.

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