Effects of flunixin meglumine, diclofenac sodium and metamizole sodium on experimental wound healing in rats

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SUMMARY

The aim of the study was to examine the effect of various nonsteroidal anti-inflammatory drugs (NSAIDs) on the healing of excisional wounding in the skin of rats. Twenty rats were equally divided among four groups. After the excisional wounding, all animals received various NSAIDs for 14 days, except control group. Repair of full-thickness excisions was followed up for 14 days and re-epithelialization, neovascularization, inflammatory cell infiltration of the wound bed, collagen deposition and percent contraction of original wound size have been evaluated as the determinants of the healing process. The percent wound closure of diclofenac and flunixin meglum treated animals was found to be significantly less compared to control group animals. Histological findings demonstrated a relative delay of healing tissue in NSAID treated animals except metamizole group. Neovascularization was significantly less in the granulation tissue of diclofenac and flunixin meglum treated groups on day 7 postwounding, than that of the controls. The mean tissue hydroxyproline contents on days 0, 7 and 14 were not statistically significant among the study groups. NSAIDs used in this animal model of wound healing caused a slight deficiency in the healing process by decreasing wound contraction, and angiogenesis which are two crucial factors in tissue integrity.

Keywords : nonsteroidal anti-inflammatory drugs - wound healing.

Introduction

The healing process in full-thickness skin wounds includes coagulation, inflammation, tissue formation, and tissue remodeling [20]. In such wounds there is an interruption of tissue continuity with destruction of all the epidermal cell layers and of mesenchymal tissue, including vascular elements. Initially, skin wounds are filled with blood and a fibrin clot. The fibrin clot is the first protection against infection [21]. In addition to providing hemostasis, the fibrin clot acts as a matrix for colonization by inflammatory cells which are attracted to the wound site via chemotaxis. Inflammation, the second phase of wound healing, occurs 1-5 days after injury. Migrating inflammatory cells accumulate in the healing wound with neutrophils predominating in the early hours of inflammation. Neutrophils help decontaminate the wound through phagocytosis of bacteria and foreign bodies. By the third day, macrophages outnumber neutrophils [20]. Macrophages engulf and phagocytose wound debris, clearing the way for the growth of new dermal matrix. Subsequently, macrophages produce angiogenic and fibrogenic growth factors that promote new tissue formation at the wound site [7].

Several studies implicate mast cells to as regulators of wound healing. The capability of mast cells to release proinflammatory mediators, as well as factors that influence cell proliferation and angiogenesis, and the accumulation of mast cells in healing wounds, have led to the assumption that mast cells are critical to the repair of injured tissue [11, 15, 43]. Re-epithelialization begins at the wound edges as early as 24 hours post injury, and granulation of the wound starts around post-injury day 5 to re-establish the integrity of the epidermis and dermis at the wound site. Granulation tissue is formed as macrophages, fibroblasts, and endothelial cells move into the wound space. Fibroblasts construct a new extracellular matrix to support cell growth while the newly formed blood vessels meet metabolic needs for the formation and maintenance of tissue. The phase of tissue remodeling

Effects de la flunixine méglumine, du diclofénac de sodium et du métamizole sodique sur la cicatrisation d’une blessure cutanée chez les rats.

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L’objectif de ce travail était d’évaluer l’effet des 3 anti-inflammatoires non stéroïdiens (AINS) : la flunixin méglumine, le diclofénac de sodium et le métamizole sodique sur la cicatrisation de plaies cutanées chez le rat. Quatre groupes de cinq rats ont été constitués. Les rats de trois groupes ont été traités pendant 14 jours après l’excision cutanée avec un AINS, le quatrième groupe étant le groupe contrôle. La cicatrisation a été suivie pendant 14 jours et appréciée grâce aux marqueurs suivants : ré-épithélisation, néovascularisation, infiltration cellulaire et diminution de la taille de la blessure. Par rapport au groupe contrôle, l’importance de la fermeture de la plaie est significativement moins importante dans les groupes “diclofénac de sodium” et “flunixin méglumine”. Les résultats histologiques ont mis en évidence un retard dans le développement du tissu cicatriciel chez les animaux traités avec le diclofénac de sodium ou la flunixin méglumine mais pas avec le métamizole sodique. À J7 après l’excision, la néovascularisation du tissu granuleux est, par rapport au groupe contrôle, significativement moins importante chez les rats traités avec le diclofénac de sodium et la flunixin méglumine. La quantité moyenne d’hydroxyproline tissulaire aux jours 0, 7 et 14 n’était pas significativement différente dans les différents groupes. Les AINS utilisés dans ce modèle animal ont entraîné une légère perturbation de la cicatrisation en diminuant deux facteurs cruciaux : la diminution de la taille de la blessure et l’angiogénèse.

Mots-clés : anti-inflammatoires non stéroïdiens - cicatrisation.
occurs as early as day 3 and may require months to be completed. Although new collagen continues to be deposited, net resorption occurs due to increased degradation of old collagen by collagenases. As macrophages begin to disappear, angiogenesis and fibroblast proliferation decrease [20].

As inflammation is central to the tissue repair process, a relationship between wound healing and anti-inflammatory drugs might be expected. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used pharmacuticals in humans and animals. The anti-inflammatory effect of NSAIDs is thought to be mainly due to the cyclooxygenases (COXs) [44]. COX proteins are the first in a cascade of enzymes that convert arachidonic acid into prostaglandins (PGs) and thromboxane (Tx), which are involved in inflammation, cancer, and embryonic development [45]. NSAIDs such as aspirin, indomethacin, naproxen, diclofenac, metamizole, and flunixin inhibit both COX-1 and COX-2 nonselectively and are widely used for the treatment of various inflammatory and noninflammatory conditions such as arthritis, cardiovascular diseases, and the management of postsurgical and post-traumatic pain in human and animals [3, 4, 23].

To investigate the role of various NSAIDs in wound repair, we have used the established model of acute excisional wounding in the skin of rats. Repair of full-thickness excisions was followed up for 14 days and re-epithelialization, neovascularization, inflammatory cell infiltration of the wound bed, collagen deposition and percent contraction of original wound size have been evaluated as determinants of the healing process, using macroscopical, biochemical, and histological techniques.

Materials and Methods

ANIMALS

Twenty male Sprague-Dawley albino rats weighing 200-250 g were used. All experimental protocols using animals were approved by the Institutional Animal Care and Use Committee at Adnan Menderes University Experimental Research Laboratory. All rats were housed under standard laboratory conditions (temperature: 23 ± 2 °C, 12 h light and dark cycles). They had free access to standard laboratory feed and water ad libitum.

EXPERIMENTAL DESIGN

The animals were randomly assigned into four equal groups (5 rats/group). After the excisional wounding, all animals received various NSAIDs for 14 days, except the control group. Group I served as controls, received physiologic saline (0.1 ml/100g body weight) per day subcutaneously. Group II received diclofenac sodium (Novartis, Istanbul) 2.5 mg/kg [30], group III received metamizole sodium (Aventis, Istanbul) 50 mg/kg [39], and group IV received flunixin meglumine (Sanofi Dogu Ilac A.S., Istanbul) 2.5 mg/kg [42] per day subcutaneously on the back. The rats were treated daily for up to 14 days with drugs, and euthanized at the end of the experiment.

EXCISIONAL SKIN WOUNDING

Rats anesthetized by ether inhalation, the hair of the dorsal skin was shaved and cleaned with povidone-iodine and dried with sterile towels. In the shaved area two circular, full-thickness excisional dermal wounds, 2 cm in diameter, was made extending through epidermis and dermis to the level of subcutaneous fat. Skin samples were collected for biochemical analysis. Skin wounds were placed on the opposite sides of midline at the scapula level. No postoperative antibiotic was used. The wounds and general health of the animals were monitored daily for up to 2 week postsurgery. No complications were encountered. The percent wound closure was recorded on day 4, 7, 11 and 14 and the wounds were photographed to measure the wound surface area. The actual value was converted into percent value taking the size of the wound at the time of wounding as 100% [37]. One biopsy comprising the total wound area and 3 mm of non wounded skin on each side was collected from each animal, bisected in the center, and prepared for histochemistry and biochemistry at days 7, and 14 after injury.

HISTOCHEMISTRY

For histological examination the samples were fixed in 10% neutral-buffered formalin and embedded in paraffin blocks. Serial sections 5 µm in thickness were taken from each block. Two adjacent paraffin sections were stained with haematoxylin-eosin for routine histological examination. Another set of two consecutive sections was stained by Masson’s trichrome to identify collagen fibers. The last set of two consecutive sections was stained by Toluidin blue for mast cell identification. Specimens were examined by an Olimpus BH2 microscope. Light microscopic examination was performed in blinded fashion, in terms of healing parameters and inflammatory changes in the granulation tissue. Epithelial regeneration, fibrin layer, edema, inflammatory cell infiltration, fibroblast proliferation, collagen deposition and angiogenesis were scored semiquantitatively using the modified Ehrlich / Hunt numerical scale [12]. The samples were graded on a score of 0 to 4 for epithelial regeneration. The scores were given as (0) no epithelium, (1) minimal epithelial regeneration, (2) single layer epithelium with partial closure, (3) moderate epithelial regeneration, and (4) multilayer epithelium with complete closure. Fibrin layer was scored as being present or absent. For the other histological parameters, five fields chosen randomly were scored for each tissue specimen at 400x magnification. A total of 10 fields were sampled per animal. The density of newly formed vessels (angiogenesis density), edema, inflammatory cell infiltration (granulocytic cell infiltration, mononuclear cell infiltration), mast cell infiltration, fibroblast proliferation in granulation tissue which was classified into four grades semi quantitatively, i.e. Grade 0=absent (no finding is present in the fields), Grade 1=slight (<25% of the fields contained evidence of any finding), Grade 2=moderate (from 25- 50% of the fields contained evidence of any finding), Grade 3=severe (>50% of the fields contained with above-mentioned histological parameters). All the specimens were examined by two researchers separately and means of the scores were calculated.

QUANTITATION OF HYDROXYPROLINE/COLLAGEN CONTENT

Tissue samples were collected on day 0, 7 and 14 and were stored in -85°C until assayed. Hydroxyproline contents in skin tissue were determined by using the modified method developed by Reddy and Enwemeka [38]. Samples were homogenized in 2N NaOH by sonication. Homogenates were hydrolysed by autoclaving at 120°C for 20 min. Chloramin-T was added to hydrolyzed samples, mixed gently and kept at room temperature for 25 min. for oxidation. Erilich’s aldehyde reagent was then added to each sample to generate a colored product which was then measured at 550 nm spectrophotometrically. BCA protein assay kit from Pierce was used to determine protein levels in tissues according to the manufacturer’s instructions. All hydroxyproline values are expressed as pg/mg protein (Mean ± SEM).

STATISTICAL ANALYSIS

Histopathologic scores of the groups were expressed as means, while percent wound closure and tissue hydroxyproline concentrations were expressed as mean ± SEM. Comparisons between experimental and control groups were performed with Kruskal-Wallis test and paired comparisons of the groups were done by Mann-Whitney U test. As we employed multiple comparisons between each group of the study (namely six), we adjusted the α using Bonferroni’s formula (α = 0.05/6=0.008) in order to avoid infected type I error [26].

Results

MACROSCOPIC ASSESSMENT

The percentage of the wound closure on days 4, 7, 11 and 14 was less in the NSAID treated animals compared to controls (Table I). The percentage of the wound closure of diclofenac treated animals on days 4, 7, 11 and 14 was found to be significantly less compared to control group animals (p=0.004). For the flunixin meglumine treated group, the wound closure was significantly less only for days 4, 7 and 11 (p=0.004). The wound closure for flunixin and diclofenac groups on days 4, 7, and 11 was also significantly less compared to the metamizole group (p=0.008). The wounds healed fastest in the control group followed by the metamizole group. Diclofenac and flunixin groups had significant delays in wound healing. The treatment of rats by these two drugs slowed the healing process which is especially evident on days 4, 7 and 11 (p=0.004).

HISTOPATHOLOGICAL ASSESSMENT

The skin structure of the rat is similar to human skin. Both are formed by dermis (connective tissue) and epidermis (epithelium), and the tissues have the same general characteristics.

Specimens harvested from the animals underwent histological assessment for epithelial regeneration, fibrin layer, edema, inflammatory cell infiltration, fibroblast proliferation, collagen content and angiogenesis (Table II).

POSTWOUNDING ON DAY 7

Control groups

The wounds were covered with a scab with severe infiltrating polymorphonuclear cells and phagocytic macrophages. In this inflammatory stage, the tissue was edematous and characterized by multiple empty spaces. The effusion was formed a thick fibrin layer, and inflammatory cells advance along lines of fibrin within a clot and along capillaries that are growing into the wound. The granulation tissue was rich with mixed inflammatory cells and neo-vascularization (Fig. 1-a). Around the neo-vascularization area, fibroplasia and collagen synthesis had begun. Epithelialization was also started at the edge of the wound (Fig. 2-a).

Treated groups

Neovascularization was significantly less in the granulation tissue of the treated groups on day 7 postwounding, than that of the controls (p=0.008) (Fig. 1-b). Fluxin and diclofenac treated animals demonstrated a relative paucity of healing tissue on seventh day. Although there were some new blood vessels present and a small number of inflammatory cells, there was minimal collagen and epithelial regeneration (Fig. 2-b). Though it was not statistically significant, edema was more pronounced in flunixin and diclofenac groups compared with controls and the metamizole group (Fig. 1-b). In contrast, metamizole-treated animals showed increased epithelial regeneration, fibroblast proliferation and collagen production compared to the other study groups. However, this finding was also statistically not significant (p>0.008). Furthermore, infiltrations of inflammatory and mast cells were less in the granulation tissue of the treated groups on day 7 postwounding, than that of the controls. The differences were statistically significant for eosinophils between...

<table>
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<tr>
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<th>Day 11</th>
<th>Day 14</th>
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<td>71.67±1.05*</td>
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<td>Flunixin</td>
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<td>29.00±1.61*</td>
<td>58.00±1.22*</td>
<td>76.00±1.87*</td>
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*: p=0.004, #: p=0.004, *: p=0.008, #: p=0.008

Table I. — Effect of metamizole, diclofenac and flunixin meglumine on % wound closure of excision wound (Values are means±SE).
FIGURE 1. — The granulation tissue on postwounding day 7. (a) The granulation tissue was rich with mixed inflammatory cells and neo-vascularization in control group (Masson’s trichrome, x10). (b) Neovascularization and inflammatory cells were less in the granulation tissue of the flunixin treated group than those of the controls (Masson’s trichrome, x10).

FIGURE 2. — Epithelial regeneration on postwounding day 7. (a) Epithelialization is visible at the edge of the wound in control group (Haematoxylin and eosin, x4). (b) There were minimal epithelial regeneration in flunixin treated group (Haematoxylin and eosin, x4). (arrow : end of the epithelialization ; asterisks : border between granulation and normal tissues).

TABLE II. — Histologic evaluation of wound healing in skin tissue. (The samples were graded on a score of 0 to 4 for epithelial regeneration. The scores were given as (0) no epithelium, (1) minimal epithelial regeneration, (2) single layer epithelium with partial closure, (3) moderate epithelial regeneration, and (4) multi-layer epithelium with complete closure. Fibrin layer was scored as being present or absent. The density of newly formed vessels (angiogenetic density), edema, inflammatory cell infiltration (granulocytic cell infiltration, mononuclear cell infiltration), mast cell infiltration, fibroblast proliferation in granulation tissue which was classified into four grades semi quantitatively, i.e. Grade 0=absent (no finding is present in the fields), Grade 1=slight (<25% of the fields contained evidence of any finding), Grade 2=moderate (from 25-50% of the fields contained evidence of any finding), Grade 3=severe (>50% of the fields contained with abovementioned histological parameters).

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<th>Granulation tissue</th>
<th>Neovascularization</th>
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<td>1</td>
<td>2,2</td>
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<td>2</td>
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<td>F</td>
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<td>2,4</td>
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<td>14</td>
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<td>M</td>
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<td>D</td>
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<td>1,8</td>
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MNC : mononuclear cell
C : Control group
F : Flunixin group
M : Metamizole group
D : Diclofenac group
the flunixin group and controls (p=0.008), and for mast cells between the diclofenac group and controls (p=0.008) (Fig. 3-a., b).

**POSTWOUNDING ON DAY 14**

**Control groups**

The scab became thin and regenerated epithelium with partial closure was observed on the surface of the healing tissue. There was no edema in the granulation tissue except for one specimen. Neovascularization and the infiltration of inflammatory cells became milder. Fibroplasia and collagen deposition was more remarkable than that of day 7 (Fig. 4-a). Collagen densities had increased, but were still different from dermal collagen bundles in unwounded dermis.

**Treated groups**

Histological findings showed that epithelial regeneration was more prominent in the metamizole group compared to the other groups on day 14 post wounding. However, this finding was not statistically significant (p>0.008). There was minimal edema in the granulation tissue of all treated animals. On postwounding day 14, neutrophil and mononuclear cell infiltrations were higher. Only flunixin group had statistically higher levels of mononuclear cells compared to the controls (p=0.008). Eosinophil infiltration was lower in treated animals compared to the controls. The presence of mast cells was higher in diclofenac group than the others (p>0.008). Fibroblast proliferation and collagen content was less in the granulation tissue of the treated groups on day 14 postwounding, than that of the controls (p>0.008) (Fig. 4-a, b). These histological findings demonstrated a relative delay of healing tissue in NSAID-treated animals except the metamizole group.

**HYDROXYPROLINE CONTENT**

Hydroxyproline as a measure for collagen was quantitated in tissue samples from the animals on day 0, 7 and 14 (Table III). The mean tissue hydroxyproline contents on day 0, 7 and 14 were not different among the study groups (p>0.008).
Discussion

The healing process following injury is one of the most fundamental defence mechanisms of an organism against its environment. Wound healing involves a series of overlapping phases, including hemostasis, inflammation, proliferation, and remodeling which together ensure an efficient closure of the wound and restore the integrity of the lost tissue. The inflammatory reaction is characterized by local edema, pain, redness, fever, and discomfort and involves the sequential infiltration of neutrophils, macrophages, and lymphocytes [20]. The basic mechanism of action of NSAIDs, prescribed to deter inflammatory discomfort, possess analgesic, antipyretic, and anti-inflammatory properties at a varying degree depending on the particular drug and the clinical condition [17]. Drugs that suppress inflammation could therefore be suspected to adversely affect wound healing.

This comparative study gives a better understanding on effects of NSAIDs during wound healing. The major categories of non-steroidal anti-inflammatory drugs include salicylates, propionic acid derivatives (ibuprofen, naproxen), phe- nylacetic acid derivatives (diclofenac sodium), pyrazolone derivatives (metamizole sodium), antranilic acids (meclofenamic acid), and the aminonicotinic acid derivative flu- nixin meglumine [14]. Previous studies have demonstrated that NSAIDs do not behave alike in their influence on wound healing [8]. Some researchers have stated that NSAIDs delayed the wound healing, whereas others claimed that the same substances had a positive effect or had no effect on the healing process. NSAIDs may affect wound healing by assisting or interfering with different phases of the processes.

Re-epithelialization, the migration of epithelial cells from the wound margin to restore epithelial continuity, is an essential process for cutaneous wound healing [5]. For healthy wound healing, there is a need for restoration of a continuous epithelial “barrier” crucial for protection of granulation tissue against mechanical injuries and infections. In our study, we observed that diclofenac and flunixin caused a slight decrease in re-epithelialization, whereas metamizole seemed to hasten epithelialization. However, this finding was not statistically significant. Similar findings have been reported by Kampfer et al. [19] showing that diclofenac markedly reduced epithelialization in excision wounds in mice. On the contrary, BLOMME et al. [2] demonstrated that diclofenac did not delay keratinocyte proliferation and differentiation in sutured skin wounds in mice, following full-thickness incisions. Similar to our observations on skin there have been studies reporting that indomethacin significantly inhibited gastric wound re-epithelialization both in vivo and in vitro conditions [24, 32, 34].

Angiogenesis, the formation of new capillary blood vessels, is a critical component of the healing process that is essential for wound healing since blood flow is necessary for oxygen and nutrients to be delivered to the healing site. NSAIDs have been shown to inhibit angiogenesis through direct effects on endothelial cells. Traditional NSAIDs may delay wound healing via decreasing prostaglandin synthesis by non-selectively inhibiting both COX-1 and COX-2, which are important in the regulation of angiogenesis [18].

Indeed, in our study, we observed that angiogenesis was less pronounced in the granulation tissue of the NSAID-treated groups, compared to controls, on day 7 postwounding (p=0.008). This difference become less visible at the later stages of the healing process. Our results are consistent with those of KAMPFER et al. [19] who reported there was no formation of vascular structures from endothelial cells within the granulation tissues of diclofenac-treated mice 5 day after excisional wounding. Furthermore, NSAIDs such as diclofenac, metamizole and indomethacin, have been shown to block angiogenesis in the ulcerated gastric tissue of rats [1, 16, 40, 41]. This inhibition of angiogenesis by NSAIDs is a causal factor in the delay of ulcer healing. On the other hand, other investigators reported no effect of diclofenac or indomethacin administration on neovascularization following full-thickness incisional, sutured skin wounding in mice [2, 29]. The difference between our study and the latter studies might be that we applied excisional wound whereas they applied an incisional one.

An adequate inflammatory response is characterized by the sequential infiltration of neutrophils, macrophages, and lymphocytes. Studies have shown that defects in the inflammatory phase of healing directly cause failure in the subsequent fibroblast growth and collagen synthesis [25, 28]. DVIVEDI et al. [10] reported that ibuprofen and diclofenac sodium noticeably reduced the cardinal histologic features of inflammation; namely macrophages, plasma cells, histiocytes and neutrophils. Likewise, DONG et al. [9] have demonstrated that ibuprofen treatment decreased neutrophil function and lymphocyte infiltration into sponges implanted in rats at the time of burn injury. Our results pointed a slight decrease in inflammatory and mast cells infiltration in the wounds of the NSAIDs treated groups on day 7 postwounding. Our findings are in agreement with BLOMME et al. [2] reporting that diclofenac caused a minimal subjective decrease in the recruitment of inflammatory cells on days 1 and 3 in full thickness incisional wounding in mice. Diclofenac sodium was also able to reduce inflammatory reactions to cat-gut [13] and cotton [35] sutures in rat subcutaneous tissues. Diclofenac sodium greatly reduced both leu-

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<td>57.20 ± 12.58</td>
<td>191.80 ± 35.50</td>
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<td>Metamizol (M)</td>
<td>291.50 ± 24.13</td>
<td>67.17 ± 10.55</td>
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<td>Diclofenac (D)</td>
<td>378.17 ± 72.84</td>
<td>142.20 ± 28.02</td>
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<tr>
<td>Flunixin (F)</td>
<td>410.33 ± 82.39</td>
<td>99.17 ± 10.91</td>
<td>163.20 ± 35.39</td>
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Table III. — Effect of metamizole, diclofenac and flunixin meglumine on hydroxyproline content (pg/mg protein) of excision wound (Values are mean±SE).
kocyte migration and lesion formation [36]. KAMPFER et al. [19], on the other hand, showed that moderate dose of diclofenac almost completely diminished infiltration of neutrophils and macrophages into the wound site in mice with excisional wounding. Diclofenac was also reported to reduce both edema and the accumulation of inflammatory cells within the paratenon in the Achilles tendon [27].

Wound healing is mainly achieved by synthesis of the connective tissue matrix. Breakdown of collagen, a major protein of the extracellular matrix liberates free hydroxyproline and its peptides. Measurement of hydroxyproline, therefore, has been used as an index of collagen turnover. The increased hydroxyproline content of the excision wounds indicates faster collagen turnover leading to rapid healing [37]. It is generally assumed that hydroxyproline content parallels the healing process. While some studies have shown that defects in the inflammatory phase of healing directly cause failure in the subsequent fibroblast growth and collagen synthesis [25, 28], some others reported that collagen deposition and cell density within the granulation tissue were not affected by NSAIDs [29]. In agreement with MÜLLER-DECKER et al. [29], we could not show difference in hydroxyproline contents from granulation tissue between treatment and control groups, in rats. Indeed, some NSAIDs have been shown to have a positive effect on soft-tissue healing where they stimulate collagen synthesis in the early phases of repair during skin and ligament healing [6]. On the contrary, MUSCARA et al. [31] showed that naproxen significantly decreased collagen deposition at the wound site in rats. They evaluated the effects of naproxen in an incisional wound model using implanted sponges and showed a decrease in hydroxyproline content, suggesting a role for naproxen in delayed wound healing via inhibition of COX-1 and COX-2 which are necessary for tissue granulation formation and remodeling. One explanation for the differences between our findings and the study of MUSCARA et al. [31] could be the models used for wound formation (excisional vs incisional). Furthermore, the NSAIDs we investigated in our study, although quite similar in mechanism of action, differ from the ones used by MUSCARA et al.

Wound contraction is another key feature of wound healing which contributes to minimization of infection and promotion of rapid wound closure. In this study diclofenac and flunixin caused significant delay in wound contraction on day 4, 7, 11, (p=0.004). However, treatment with metamizole resulted in a slight decrease in contraction when compared with the controls. Other researchers have found similar results using different drugs ibuprofen, phenbutazone, aspirin, indomethacin, in similar rat excisional wound models during first or second week [8, 22]. DIWAN and KULKARNI [8] also showed that enfenamic acid, another NSAID did not retard wound contraction at any stage if anything, it appeared to marginally promote the process. This compound also hastened epithelization. OGIHARA and OKABE [33] reported that the repeated administration of indomethacin delayed the healing in acetic acid-induced gastric ulcers in rats via inhibiting the contraction of the ulcer base.

In summary, our findings indicate that NSAIDs used in this animal model of wound healing caused a slight deficiency in the healing process by decreasing wound contraction, and angiogenesis which are two crucial factors in tissue integrity. Microscopic examination showed no significant difference in collagen production and cell infiltration in the granulation tissue. These data suggest that NSAIDs should be used judiciously to minimize their adverse effects on wound healing in humans.

References
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