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Original Research Article

A comparative study of the effect of piroxicam versus diclofenac on wound healing in clean abdominal wounds

Chandrashekar Reddy J. Madinur[1], Prashant Tubachi[2]*, A. S. Godhi[3]

[1]Department of Surgery, Navodaya Medical College, Raichur, Karnataka, India
[2]Department of General Surgery, SDM Medical College and Hospital, Sattur, Dharwad, Karnataka, India
[3]Department of General Surgery, JNMC Belgaum, Karnataka, India

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***Correspondence:**
Dr. Prashant Tubachi,
E-mail: tubachi9@gmail.com

ABSTRACT

Background: The primary function of the skin is to serve as a protective barrier against the environment. The process of wound healing constitutes an array of interrelated and concomitant events. Understanding these processes and various factors affecting these processes continue to expand. The present study was undertaken to compare and evaluate the effect of piroxicam versus diclofenac on wound healing in clean abdominal wounds.
Methods: The present one year randomized controlled trial was conducted on all the patients undergoing appendicectomies for uncomplicated appendicitis and uncomplicated inguinal hernia repairs in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of one year. Based on the thumb rule a total of 60 patients divided into two groups of 30 each were studied. Based on the computer-generated randomization patients were allocated to two groups that is group A (Inj. Piroxicam) and Group B (Inj. Diclofenac).
Results: In the present study, males outnumbered females with male to female ratio between of 1.72 to 2:1. The mean age in group A was30.9±7.86 years and in group B it was 30.3±7.97 years. Both the groups that is Group A and B were graded under grade I (Good wound healing) from the POD 3 onwards. Overall the individual score and total scores had no influence of the final grading (outcome) of the wound.
Conclusions: Overall, better results were seen on wound healing in patients who received Inj piroxicam with significantly less post-operative redness and edema. However, this did not have significant difference in the final outcome of the grading of the wound.

Keywords: Diclofenac sodium, Piroxicam, Wound healing

INTRODUCTION

The primary function of the skin is to serve as a protective barrier against the environment. Loss of the integrity of large portions of the skin as a result of injury or illness may lead to major disability or even death.[1]

The wound healing is a complex process that can be divided into inflammatory reaction, proliferation and maturation of newly formed tissue. The inflammatory phase involves vascular and cellular events and is best characterized by edema, erythema and marked increase of blood supply. During proliferative phase there is formation of the epithelium with concomitant growth of granulation tissue and new blood vessels (angiogenesis). Angiogenesis seems to be strictly coordinated and regulated by multiple growth factors and cytokines released at the wound site. Once the tissue within the

wound is formed the maturation phase begins. The synthesis of collagens and other extracellular matrix components increases tensile strength of the wound. Thus, the final result of the process of healing is the formation of tissue which tries to replicate the normal, uninjured skin.[2]

This process can go awry and produce an exuberance of fibroblastic proliferation with a resultant hypertrophic scar, which by definition is confined to the wound site. Further exuberance can result in keloid formation, where scar production extends beyond the area of the original insult. Conversely, insufficient healing can result in atrophic scar formation.

It is postulated that, NSAIDs by their anti-inflammatory action may impair wound healing which may explain why they have been used to only a limited extent to relieve pain.[3] If they are to have maximal effect they must be started before the operation.

Inhibition of matrix metalloproteinases (MMPs) promotes early wound healing by increase in the tissue permeability around the wound. Piroxicam is a known NSAID. Which is known to inhibit matrix metalloproteinases. Hence unlike other NSAIDs, Piroxicam is likely to promote wound healing. However, there is limited data to support this hypothesis. Hence the present study was undertaken to compare and evaluate the effect of piroxicam versus diclofenac on wound healing in clean abdominal wounds.

METHODS

The present one year randomized controlled trial was conducted on all the patients undergoing appendicectomies for uncomplicated appendicitis and uncomplicated inguinal hernia repairs in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of one year. Based on the thumb rule a total of 60 patients divided into two groups of 30 each were studied. Based on the computer-generated randomization patients were allocated to two groups that is group A (Inj. Piroxicam) and Group B (Inj. Diclofenac).

Patients were allocated to two groups according to randomization procedure that is group A which received injection piroxicam and group B which received injection diclofenac.

All the patients received injection ciprofloxacin 500mg twice daily for one day and Inj ornidazole 500mg twice daily for one day, followed by tablet ciprofloxacin-ornidazole twice daily for four days.

The first dose of Piroxicam (40mg) or Diclofenac (75mg) was administered on the day of the operation according to their groups respectively three to four hours after surgery which was defined as the day zero.

The patients received a single daily intramuscular injection of two ml Piroxicam (40mg) or intramuscular injection of three ml Diclofenac (75mg) on day one followed by single injection of piroxicam (20mg) one ml intramuscularly or Diclofenac (75mg) three ml intramuscularly on day two.

Wound was inspected on third, fifth, seventh and fourteenth post-operative day. Based on the gross appearance the surgical wound was assessed. The characteristics of the wound were assessed and evaluated based on Degree of swelling, Oozing, Necrosis of wound edges, Redness and Edema. They were graded zero to three.

Based on these characteristics the wound healing was graded as:[3]

- Good wound healing (0-5)
- Average wound healing (6-12)
- Poor wound healing (13-18)

End point of study was whether the wound heals with or without infection before fourteenth day of surgery.

Statistical analysis

Data obtained was tabulated and expressed as rates, ratios and percentages. Comparison was done by applying chi-square and Fisher's exact test. A probability value ('p' value) of less 0.05 was considered as statistically significant.

RESULTS

In the present study, males outnumbered females with male to female ratio between of 1.72 to 2:1. The mean age in group A was 30.9±7.86 years and in group B it was 30.3±7.97 years (Table 1). Among patients in group A, swelling was not seen on post-operative day (POD) 3 whereas in group B 3.3% had swelling. 80.0% of patients in group A and 16.7% of Group B patients were free from redness on POD 3 (Table 2). On POD 5 all the patients in Group A were free from redness compared to 50% in Group B (Table 3).

Table 1: Mean age group comparison.

	Mean age	
	Mean	**SD**
Group A	30.9	7.86
Group B	30.3	7.97

x^2=0.310 DF=58 p=0.758

On post-operative day three, edema score of 1 and 2 in 53.3% and 6.7% of patients in group B was noted respectively compared to 6.7% of patients in group A who had a score of 1. On post-operative day 5 all patients in Group A were free from edema when compared to

76.7% of patient in group B (Table 4). On post-operative day seven, patients in both the groups had no edema. Also, oozing, necrosis of wound edges and hematoma formation was not seen in both the groups.

Table 2: Degree of swelling on POD 3.

Degree of swelling	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
0	30	100.0	29	96.7
1	0	00	1	3.3
Total	30	100	30	100

p=1.000 (Fisher's exact test)

Among patients in group A on post-operative day three 73.3% patients were free from all the symptoms and all the patients (100%) were free from all the symptoms on post-operative day five suggesting significantly better results in group A ($p<0.05$). Whereas, in group B majority of the patients (40%) had a total score of 1 on post-operative day three, 50% of patients had a total score between 1 to 3 on post-operative day five and symptoms persisted in 20% of patients on post-operative day seven.

In this study both the groups that is Group A and B were graded under grade I (Good wound healing) from the POD 3 onwards. Overall the individual score and total scores had no influence of the final grading (outcome) of the wound.

Table 3: Redness on POD 5.

Redness	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
0	30	100.0	15	50.0
1	0	00	14	46.7
2	0	00	1	3.3
Total	30	100	30	100

p=0.000 (Fisher's exact test)

Table 4: Edema on POD 5.

Edema	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
0	30	100	23	76.7
1	0	00	7	23.3
2	0	00	0	00
Total	30	100	30	100

p=0.011 (Fisher's exact test)

DISCUSSION

The process of wound healing constitutes an array of interrelated and concomitant events. Understanding these processes and various factors affecting these processes continue to expand.

Tremendous advancements have been made in understanding the process of wound healing. The cell types and the order in which they appear in the wound have been established; many growth factors and their functions have been demonstrated.[4] Despite the advances in understanding the science of wound healing, many more steps have yet to be discovered and illustrated. The frontier of this field includes the prevention of hypertrophic and keloid scar formation and, ultimately, any visual remnant of the wound.

Drugs such as NSAIDs, COX-2 inhibitors, corticosteroids, DMARDs and biologic response modifiers affect inflammation and local immune responses, which are necessary for proper wound healing in the perioperative setting, thereby potentially resulting in undesirable postoperative complications. Such complications include wound dehiscence, infection, and impaired collagen synthesis. The end result is delayed healing of soft tissue.[5]

For certain drugs, such as methotrexate, trials have been conducted in humans, whereas, with other drugs, either small-animal studies on wound healing are available.[5]

In some cases, discontinuation of therapy may be required up to four weeks before surgery because of the long half-lives of the drugs. In doing so, patients may experience an exacerbation or worsening of disease. Individual patient should be evaluated for risk factors, disease severity, and the pharmacokinetics of available therapies weighing the risks and benefits of discontinuing therapy in the perioperative setting.[6]

Patients with rheumatoid arthritis may already be at increased risk of impaired wound healing because of a reduction in skin thickness that occurs independently of corticosteroid use. Patients with rheumatoid arthritis are also generally at greater risk of infection and vasculitis.[7-10] The presence of diabetes mellitus may predispose patients to infection, typically from compromised microvascular blood flow and higher serum glucose levels, which may impair the ability of neutrophils to fight infection.[11-13]

Immuno-suppressed patients, such as those who are positive for the human immunodeficiency virus or are treated with chemotherapy, will undoubtedly experience increased rates of infection. Peripheral arterial disease may also contribute to poor wound healing because of a reduction in blood flow and tissue perfusion. Patients who are deficient in vitamin C or are taking other drugs such as anticoagulants, tetracycline, or erythromycin are predisposed to infection.[13-15]

Piroxicam is an N-heterocyclic carboxamide of 1,2 benzo thiazine 1,1 dioxide with analgesic and anti-inflammatory activity. It is a potent acidic anti-inflammatory agent structurally distinct from the current agents such as indomethacin, phenylbutazone or naproxen. Pharmacokinetic studies indicate a longer plasma half-life for piroxicam than for these agents. The high potency,

long half-life and absence of cardiovascular or central nervous system effects have encouraged clinical trials of piroxicam.[16] Hence the present study was undertaken to compare and evaluate the effect of piroxicam versus diclofenac on wound healing in clean abdominal wounds. There are various reasons to suspect that NSAIDs would impair wound healing, because inflammation is the process whereby cells are recruited to remove necrotic debris and to initiate healing.[16] In the case of NSAID piroxicam, however, there are animal studies indicating that the opposite may be true.[17,18]

In a previous study, authors induced injuries of the musculotendinous junction in rats and discovered that treatment with piroxicam had a positive effect on healing and delayed the stress failure of the muscle tendon attachment.[17] Eleven days after the wound was induced, the rats receiving piroxicam had stronger and stiffer muscles that the untreated controls, an effect that may be partly explained by an increase in collagen metabolism. Similarly, medial ligament of the knees of male Sprague-Dawley rats were injured and it was found that, administration of piroxicam during the first six days after injury resulted in a 42% increase in ligament strength by day 14 relative to placebo treated controls ($p<0.01$).

The results of animal studies such as these suggest that an investigation of the effects of piroxicam on wound healing should be extended to humans.[17,18] Hence, the present one year randomized controlled trial was conducted on all the patients undergoing appendicectomies for uncomplicated appendicitis and uncomplicated inguinal hernia repairs in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. Based on the thumb rule a total of 60 patients divided into two groups of 30 each were studied. Based on the computer-generated randomization patients were allocated to two groups that is group A (Inj. Piroxicam) and Group B (Inj. Diclofenac).

In the present study, males outnumbered females as discussed in results. Mean age group was comparable in both groups. Similar study comparing piroxicam with placebo from Belgium reported 56% males and 44% females in placebo group and 46% males and 54% females in piroxicam group.

In the present study among patients in group A, swelling was not seen on post-operative day (POD) 3 whereas in group B 3.3% had swelling. However, this difference was not statistically significant ($p=1.000$).

In the present study, 80.0% of patients in group A and 16.7% of Group B patients were free from redness on POD 3. In the remaining, 73.3% and 10.0% of patients in group B had redness score of 1 and 2 respectively compared to 20% of patients in group A who had a score of 1. This difference was statistically significant ($p<0.0001$). On POD 5 all the patients in Group A were free from redness compared to 50% in Group B. In the remaining 46.7% and 3.3% of patients in group B had redness score of 1 and 2 respectively ($p<0.0001$). On POD 7, 20% of patients in group B had redness score of 1 ($p=0.024$).

In the present study on post-operative day three edema score of 1 and 2 in 53.3% and 6.7% of patients in group B was noted respectively compared to 6.7% of patients in group A who had a score of 1. This difference was statistically significant ($p<0.0001$). On post-operative day 5 all patients in Group A were free from edema when compared to 76.7% of patient in group B. Edema score of 1 was seen in 23.3% of patients in group B. This difference was statistically significant ($p=0.011$). On post-operative day seven, patients in both the groups had no edema. Also, oozing, necrosis of wound edges and hematoma formation was not seen in both the groups. Overall better results were seen in patients with group A with significantly less redness and edema.

In the present study majority among patients in group A on post-operative day three 73.3% patients were free from all the symptoms and all the patients (100%) were free from all the symptoms on post-operative day five suggesting significantly better results in group A ($p<0.05$). Whereas, in of surgical wound healing have not been reported frequently in the literature.[3]

Future advances in wound healing will focus on affecting the agents that influence the processes involved in the repair of damaged tissue. Laser techniques, non-laser techniques, and other modalities are being explored to enhance the proliferation of cells, the migration of cells, and the acceleration of the healing of wounds.[19,20]

Human cell-conditioned media developed in embryologic like conditions has been shown to improve healing times in post laser facial skin.[21] Fetal tissue can heal scar less due to the unique characteristics of fetal epithelial and mesenchymal cells and the functioning of the fetal immune system.[22] Hyperbaric oxygen has also been used to promote healing.[23] Stem cells, in particular adipose-derived stem cells, have been shown to ameliorate wound healing, and continued research in these areas appears promising.[24,25]

CONCLUSION

Overall, the present study showed better results on wound healing in patients who received Inj piroxicam with significantly less post-operative redness and edema. However, this did not have significant difference in the final outcome of the grading of the wound.

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