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Single Blind, Comparative Study of Ketoprofen Cream Vs Diclofenac and Piroxicam Cream in Management of Rheumatoid Arthritis Patients

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ABSTRACT

Non steroidal Anti- inflammatory drugs have their origin as the derivatives of plants, which were observed to have their therapeutic effects in different disease states. They have the advantage of local action without developing central adverse effects and cognitive impairments. Side effects have been well described, although partly neglected. Topical delivery of NSAID has its therapeutic applications in management of pain and inflammation in Rheumatoid Arthritis patients. Rheumatoid Arthritis is a chronic systemic inflammatory disorder that may affect many tissues and organs but principally attacks the synovial joints. It can be disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. The aim of the present investigation was to compare the Ketoprofen cream with Diclofenac and Piroxicam cream in a group of volunteers suffered from Rheumatoid Arthritis and to compare the efficacy of these creams in reduction of inflammation. This single blind comparative study was done to determine the efficacy, tolerability and acceptability of topical application of Ketoprofen cream (1%w/w) vs diclofenac cream (1% w/w) and piroxicam cream (0.5% w/w) in Rheumatoid Arthritis patients. In this study one hundred and twenty five volunteers suffering with acute Rheumatoid arthritis and age group between 40-70 years were analyzed for assessing the intensity of pain and anti-inflammatory effects of these three creams. The study revealed that Ketoprofen cream provides a good level of pain relief removes swelling and tenderness and improves the functional impairment, without the systemic adverse events associated with oral NSAIDs.

Keywords: Cream, Diclofenac, Ketoprofen, Piroxicam, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid Arthritis is an autoimmune progressive disorder that leads to the destruction of cartridge, bone and ligaments causing deformity of joints [1]. The cause of Rheumatoid Arthritis is unknown. . It is believed that the tendency to develop Rheumatoid Arthritis may be genetically inherited (hereditary). Certain genes have been identified that increase the risk for Rheumatoid Arthritis [2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain and inflammation in Rheumatoid Arthritis patients, but their use comes at the cost of toxicity, with a 2-4% annual incidence of serious gastrointestinal ulcer and complications—four times higher than in non-users [3]. NSAIDs have been applied topically for decades. This route possibly reduces gastrointestinal adverse reactions by maximizing local delivery and minimizing systemic toxicity [4]. Ketoprofen, Diclofenac and Piroxicam are the drugs included in the class of Non-Steroidal Anti-Inflammatory drugs (NSAIDs), each drug has a specific tissue distribution and pharmacodynamics [5]. They block the inflammatory cascade and cycloxygenases (COX) by inhibiting prostaglandin and thromboxane production and lead to reduction in pain, fever, platelet aggregation and inflammatory response [6]. Besides inhibiting the prostaglandin and thromboxane production, Ketoprofen also inhibit rabbit neutrophil and human lung lipoxygenase activity [7]. NSAIDs like Ketoprofen, Diclofenac and Piroxicam are generally indicated for

symptomatic relief of Rheumatoid arthritis, Osteoarthritis [8], Inflammatory Arthropathies (Ankylosing Spondylitis, Psoriatic Arthritis), Gout [9], Metastatic bone pain, Dysmenorrhoea [10], Post operative pain, Migraine and Headache. The use of oral preparations of NSAIDs increase the risk of gastrointestinal and cardiovascular complications compared with non NSAIDs users [11]. Reduction of adverse drug reactions associated with the use of topical preparations of NSAIDs is being well considered to obtain high patient compliance and drug therapy efficacy [12]. Substantial data suggests that topical NSAIDs have pain-relieving properties in Rheumatoid Arthritis disease. An important sign of the increasing importance of using topical medication is that the European League against Rheumatism and the International Osteoarthritis Research Society state that topical NSAIDs are preferred over oral NSAIDs for mild-to-moderate hand and knee Osteoarthritis, in patients with sensitivity to oral compounds [13]. In addition, the UK NICE guidelines for knee and hand Osteoarthritis recommend use of paracetamol and/or topical NSAIDs over oral NSAIDs, COX2 inhibitors, and opioids [14].

MATERIALS AND METHODS

Human Volunteers:

Total number of volunteers: 125
Gender: Male and Female
Age: 40-70 years

Cream Formulations:

Ketoprofen Cream (1% w/w) [15]
Diclofenac Cream (1% w/w) [16]
Pioxicam Cream (0.5% w/w)

Methods:

This is a single blind, randomized comparative trial conducted at three different locations:
Bajwa Trauma Centre, Sargodha, Pakistan
Amin Orthopedic Centre, Sargodha, Pakistan
National Hospital, Faisalabad, Pakistan

One hundred and twenty five volunteers were divided into three groups receiving Ketoprofen cream, Diclofenac cream and/or Piroxicam cream. The volunteers were given written instructions to apply the cream regularly on affected area in a dose of 4 inches 3-4 times a day up to 14 days. Volunteers both (males & non- pregnant females) between the ages of 40-70 suffered from Acute Rheumatoid Arthritis were included in this study.

Inclusion Criteria for Study:

- The volunteers were 40-70 years of age
- The volunteer was diagnosed with uncomplicated Acute Rheumatoid arthritis
- The site of injury was accessible to the volunteer so that he/she can apply the study medication himself/herself
- The volunteer must met the pain entry criteria
- The volunteer was willing to discontinue use of any pain medication not provided as a part of study

Exclusion criteria for study:

- The volunteer has active skin lesions at the intended site of application of study medication. Skin lesions include open wound, rash, papules, vesicles and erythema associated with the site of injury
- The volunteer has used any form of opioids since the time of injury
- The volunteer has taken any form of steroids within 30 days prior to enter into study
- The volunteer has done non- pharmacological treatment of injury
- The volunteer has experienced any kind of allergy to Ketoprofen, Diclofenac or Piroxicam
- The volunteer has participated in an investigational drug study or received an investigational drug within a period of 30 days prior receiving the study mediation

Recent injuries sustained within 4S hours (not requiring surgical treatment) were included under "acute" category. Written informed consent was obtained prior to enrollment of patients in the study. The patients were evaluated before initiation of therapy and then at day 1, day 4, day 8 and day 14 of the therapy for the following parameters.

1. Pain:

Onset of pain: pain intensity on a 10cm visual analogue scale (0-worst ever, 10-best ever); pain at rest, passive movement, palpation and isometric contraction on a 4 point scale (0-absent, 1-mild, 2-moderate, 3-severe)

2. Tenderness:

Tenderness on a 4 point scale (0-not tender, 1-tender, 2-winced, 3-withdrew)

3. Swelling:

Swelling on a 4 point scale (0-absent, 1-mild, 2-moderate, 3-severe)

4. Functional Impairment:

Functional impairment on 5 point scale: (o-none, 1 mild, 2 moderate, 3 marked & 4 severe)

Paracetamol was given as rescue drug in case the pain relief by topical formulations was inadequate. The amount of paracetamol intake was recorded as indirect measurement of effectiveness of the trail drugs.

RESULTS AND DISCUSSION

A total of 125 patients of aged between 40-70 years were enrolled in this study. However 15 patients were lost to follow up and only 110 patients were evaluated. A total of 45 patients received Ketoprofen cream, 35 received Diclofenac cream and 30 received Piroxicam cream. The ratio of males to females in the study was 19:25 (48/62). The patient's demographics of all three groups were comparable.

Table 1. Patient Demographics

Parameters	Ketoprofen Cream	Diclofenac Cream	Piroxicam Cream
Total no. of patients	45	35	30
Sex:			
Male	22	15	11
Female	23	20	19

Within the group all the three groups had improvement in the various parameters studied (onset of pain; pain intensity on a 10 cm VAS; pain at rest, passive movement; palpation and isometric contraction; swelling; tenderness: and functional impairment). This improvement was statistically significant when compared at the beginning and end of the therapy. However, over the study period of 14 days there was no significant change in the paracetamol intake in all the three groups.

The onset of pain relief was observed between 1-2 hours. In some cases the onset of pain relief was quite delayed but there was not much difference between groups. The between group analysis showed that treatment with Ketoprofen cream was significantly more effective than Diclofenac cream and clinically better than Piroxicam cream. The pain intensity on 10cm visual analogue scale was best ever 98% with Ketoprofen cream group, 80% with Diclofenac cream and 84% with piroxicam cream group at the end of therapy. The pain intensity mean score of 9.77cm (when assessed on 0-10 cm VAS) for Ketoprofen cream was statistically more significant ($p<0.01$) than Diclofenac and Piroxicam cream whose mean scores were 8.01and 8.44 respectively indicated by number 1 on x-axis in Fig I.

At day 14, 98% improvement was seen in patients with pain at rest with Ketoprofen cream, 82% with Diclofenac cream and 84% with Piroxicam cream. Pain at passive motion was improved up to 96% with Ketoprofen cream than 82% and 84% with Diclofenac and Piroxicam groups respectively. Pain at palpitation and isometric contraction was improved upto 90% and 88% with Ketoprofen cream group respectively, 80% and 78% with Diclofenac cream group respectively and 82% and 80% with Piroxicam cream respectively as shown by number 2, 3, 4 and 5 on x-axis in Fig I.

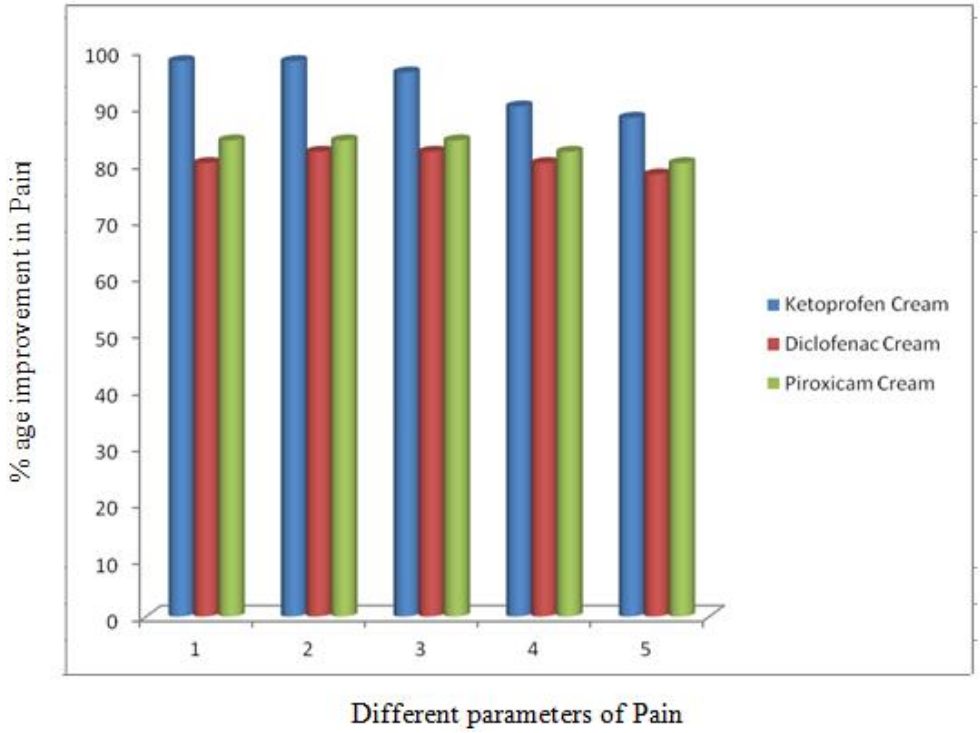

Figure 1. Improvement in Pain over 14 days study period

Table 2. Comparative evaluation of different Creams over 14 days period

Day Characteristics	Ketopofen Cream (n = 45)				Diclofenac Cream (n = 35)				Piroxicam Cream (n = 30)			
	1	4	8	14	1	4	8	14	1	4	8	14
Pain Intensity on VAS (cm)	4.15	6.29	7.55	9.77	3.75	4.88	6.29	8.01	3.99	5.01	7.0	8.44
Pain at Rest	2.1	1.8	0.7	0.1	2.1	1.9	1.2	0.9	2.1	1.8	1.2	0.8
Pain on passive Motion	2.3	1.9	0.9	0.2	2.3	2.0	1.4	0.9	2.3	1.9	1.3	0.8
Pain on palpation	2.7	2.1	1.2	0.5	2.7	2.2	1.7	1.0	2.7	2.1	1.6	0.9
Pain on Isometric Contraction	3.0	2.4	1.5	0.6	3.0	2.6	1.9	1.2	3.0	2.5	1.6	1.0
Tenderness	2.5	1.8	0.9	0.2	2.5	2.0	1.3	0.8	2.5	1.9	1.1	0.6
Swelling	3.0	2.1	1.4	0.3	3.0	2.4	1.8	1.0	3.0	2.2	1.5	0.8
Functional Impairment	3.5	2.6	1.6	0.5	3.5	2.9	2.0	1.1	3.5	2.8	1.9	0.9

Clinically tenderness was absent upto 96% in Ketoprofen cream group, 92% in Diclofenac cream group and 94% in Piroxicam cream group representated by number1 on x-axis in Figure 2. Absence in swelling was observed 94% with Ketoprofen cream group as compared to 80% and 84% with Diclofenac and Piroxicam group at the end of therapy. Functional improvement was seen 90% with Ketoprofen cream group than 78% and 82% with Diclofenac and Piroxicam cream groups respectively as shown in Figure 2.

No statistically significant difference was observed in the Paracetamol intake between the three groups.

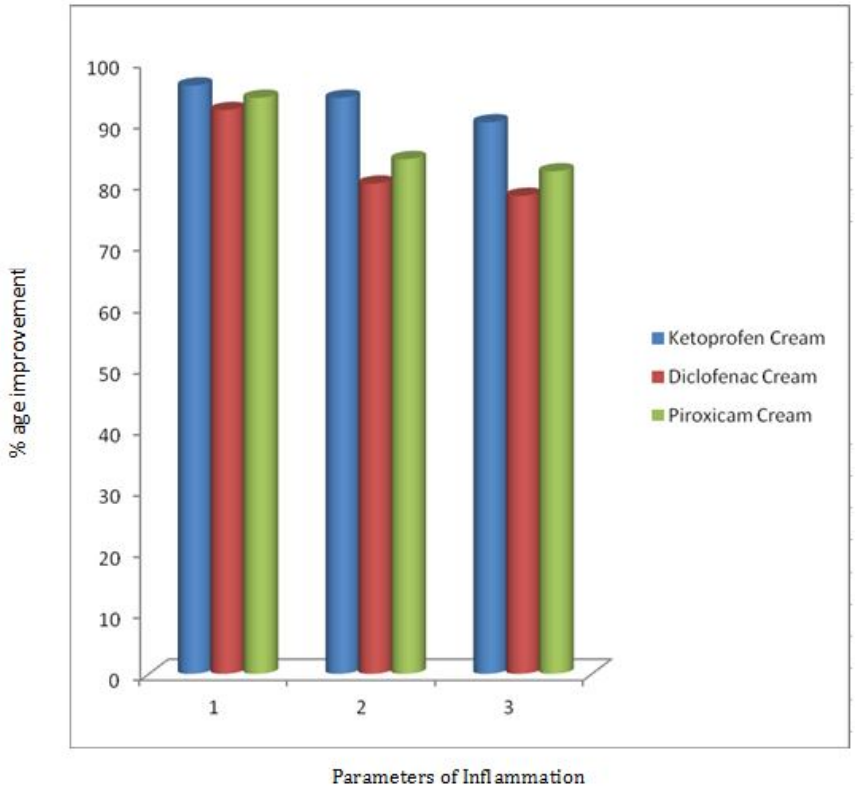

Figure 2. Improvement in Inflammation over 14 days study period

CONCLUSION

Ketoprofen, Diclofenac and Piroxicam all three are NSAIDs that exhibit analgesic, antipyretic and anti-inflammatory activities. From the above results it can be concluded that on day 14 Ketoprofen cream was statistically better ($p<0.01$) in reducing pain, tenderness, and swelling and improves the functional ability than Diclofenac cream. Piroxicam cream rated better ($p<0.05$) in these parameter as compared to Diclofenac cream.

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