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Research Article

A Randomized Clinical Study of Topical Ketorolac Tromethamine Gel and Topical Ketoprofen Gel in Patients with Knee Osteoarthritis or Low Back Pain

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Abstract

Introduction: Musculoskeletal pain is one of the major reason for patients visiting hospitals and pharmacies hampering the quality of life of patients. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely recommended and used in the management of pain syndromes associated with musculoskeletal disorders.

Following study was conducted to study the efficacy and safety of topical Ketorolac tromethamine (2%) gel and topical ketoprofen (2.5%) gel in patients with knee osteoarthritis or low back pain.

Materials and Method: This open label, randomized parallel group study enrolled 240 adult patients: 120 with lower back pain and 120 with knee osteoarthritis (Gonarthrosis). Patients received topical application of Ketorolac gel or Ketoprofen gel on the affected area thrice daily for 10 days, respectively. Efficacy was evaluated on the Visual Analog Scale and safety was assessed. Trial registered at Clinicaltrial.gov with registration number NCT02638831.

Results: In patients with knee osteoarthritis the reduction in visual analog score (VAS) for pain at rest in Ketorolac gel group and Ketoprofen group was 23.73 mm and 14.73 mm respectively. Reduction in VAS for pain at motion was 28.69 mm and 14.8 mm in Ketorolac and Ketoprofen group respectively (< 0.05). The reduction in pain at motion was significantly better with Ketorolac tromethamine gel as compared to Ketoprofen gel in patients with Knee osteoarthritis.

Similarly, in patients with Low Back Pain the change in at VAS for pain at rest in Ketorolac gel group and Ketoprofen group was 14.8 mm and 10.55 mm respectively. Change in VAS for pain at motion was 33.23 mm and 29.42 mm in Ketorolac and Ketoprofen group respectively.

In course of evaluation tolerability, "Excellent" and "Good" was noted in 98% patients in "Ketorolac" group, while 73% in "Ketoprofen" group (p = 0.0003).

Conclusion: Ketorolac gel has better analgesic effect versus ketoprofen, with favorable safety profile. Ketorolac gel is an effective option for the treatment of diseases of the musculoskeletal system accompanied by moderate pain.

Keywords: *Anti-Inflammatory Gel Agents; Non-Steroidal; Pain; Knee Osteoarthritis; Low Back Pain*

Abbreviations

NSAIDS: Non-Steroidal Anti-Inflammatory Drugs; VAS: Visual Analog Score

Introduction

Osteoarthritis is the major cause of disability affecting a vast population of people.. Osteoarthritis affects approximately 2% people above age 18 years and 25% of the Russian population above the age of 38 years. Also, 50% of these elderly patients have limited ability to move [1-3]. In general practice, patients with diseases of the musculoskeletal system are common and musculoskeletal diseases takes the second place by days and the third place by temporary inability to work among all the classes of diseases.

Various guidelines have recommended the use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in the management of Osteoarthritis [4-8]. Oral NSAIDs are widely used to relieve the painful syndromes but are also associated with the systemic toxicity that can affect the gastrointestinal, renal and cardiovascular system of the patients [9-12]. Speed of onset of action and effective pain relief are the mainstay of medical treatments for acute musculoskeletal conditions. Use of topical NSAIDs to treat acute musculoskeletal conditions has become widely accepted and also recommended by guidelines [4,6]. because they provide pain relief with limited systemic exposure and associated adverse events [13,14]. Topical products containing diclofenac, ibuprofen, ketoprofen, indomethacin, phenylbutazone, piroxicam, Ketorolac are available in Russia for the management of painful musculoskeletal disorders.

The manifestation and rate of treatment effect depends upon active substance and dosage form. It is recommended to use topical dosage forms of NSAIDs which can penetrate deep into the skin and subcutaneous tissue thereby effectively blocking the pain pathway. The most successful form for topical therapy is gel which contains alcohol as solvent assuring rapid absorption of active substance in superficial structures of the joint. Thus, the administration of gel is more efficient in comparison with ointments or creams [14,15].

Ketorolac Tromethamine is a topical NSAID used to treat musculoskeletal pain syndromes in Russia. The drug composition includes enhancing agents and pH-systems to optimize the permeability. As comparative tests of different agents - penetration enhancers - demonstrated that dimethyl sulfoxide, oleic and citric acids significantly increase the permeability of Ketorolac into the skin. This dosage form was developed and is intended to arrest pain caused by inflammatory processes being devoid of any risk of GI adverse effects which are often observed with oral NSAIDs [16].

There is limited data available on use of topical ketorolac gel in patients with gonarthrosis or low back pain. We conducted the following study to evaluate and compare the efficacy and safety of topical Ketorolac gel with ketoprofen gel in patients with musculoskeletal pain, particularly gonarthrosis and low back pain. This Trial is registered at clinicaltrials.gov under registration number NCT02638831.

Materials and Methods

Participants and Study Design

This was a multi-centered, open label, prospective, randomized study. Total 240 patients of both genders with gonarthrosis (120) or low back pain (120) were included in the study. Patients with pain intensity according to visual analog scale (VAS) ≥ 40 mm at rest or ≥ 50 mm in movement were included. In the gonarthrosis group, patients of 40 to 70 years diagnosed with gonarthrosis according to Clinical American College of Rheumatology classification criteria of knee arthritis (R Altman., *et al*. 1986) were included. For the group with low back pain, patients aged 20 to 65 years with acute pain in lower back (less than 12 weeks) or exacerbation of chronic back pain (more than 12 weeks) were included. Pregnant women, patients who experienced serious adverse events with study drugs earlier were excluded from the study. All patients were prohibited to use any additional topical therapy or systemic NSAIDs.

Within the study groups of gonarthrosis and low back pain, patients were randomized 1:1 to Ketorolac 2% gel or Ketoprofen 2.5% gel. The gels was applied as a column of gel about 3 - 5 cm for 10 days and followed up for 14 days.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). All patients provided signed informed consent prior to the start of the study in accordance with local regulations.

Outcome Measures

Intensity of pain at rest, in movement, overall patient's condition by physician and patient assessment were assessed by visual analog scale (VAS, mm). Compliance to drug therapy was also assessed.

All patients who completed the study underwent evaluation of efficacy on Day 10. The evidence of comparable efficacy of the drugs is based on calculation of 95% confidence interval for the difference of the means of VAS at rest during the last visit.

Evaluation of the safety of the drugs under study was conducted during the entire course of the study based on clinical observation and laboratory indicators. It was carried out on the basis of the number of adverse events recorded during the study and patient evaluation of tolerance.

Statistical Methods

The sample size of the study was calculated based on the hypothesis of non-inferiority of Ketorolac gel in comparison with the Ketoprofen gel. With a power of 80% and type I error ≤ 0.05, 113 patients in each parallel group were required. Considering the dropout rate of 5%, the total sample size required was 240 patients (120 patients each in each therapy group). Data was compared using T-test. Frequency of adverse effects were analyzed using Fisher exact test. Calculations were done using programs G*Power 3.14 and Statistica 7.0.

Results and Discussion

Results

The mean age (Standard Deviation, SD) of patients in Ketorolac and Ketoprofen group was 52.5 (± 11.3) and 52.5 (± 11.0) respectively. The patient distribution in the study is outlined in figure 1. The groups were similar with respect to baseline characteristics. Summary of demographic data of patients participating in the study is presented in table 1.

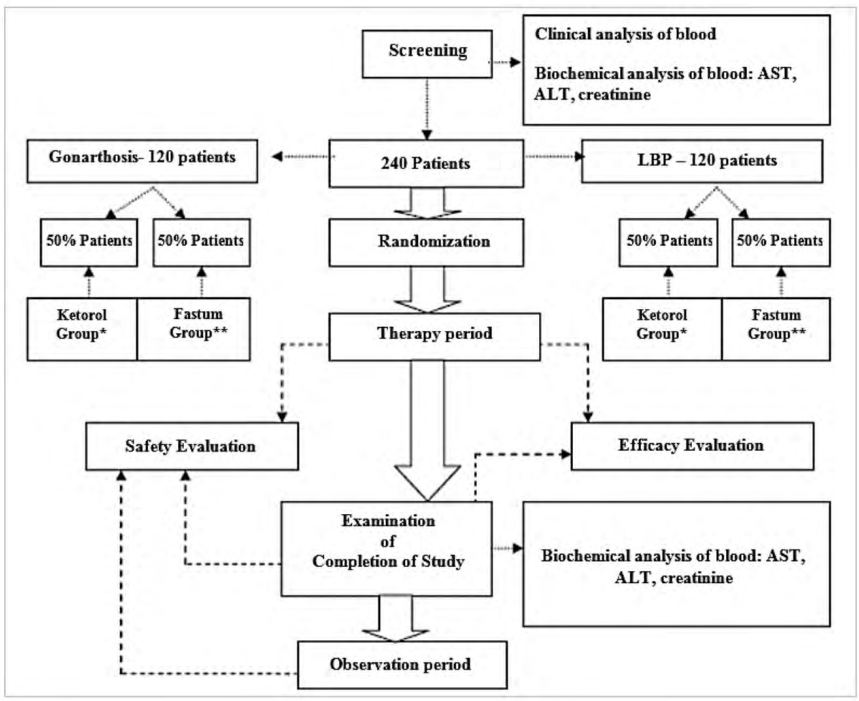

Figure 1: *Study Flow.*

Parameters	Ketorolac n = 120	Ketoprofen n = 120	Value of p
Patient Demographics			
Age, years	52.5 ± 11.3	52.5 ± 11.0	p = 0.64
Height, cm	167.2 ± 6.9	169.7 ± 7.6	p = 0.73
Weight, kg	78.7 ± 14.7	81.5 ± 13.6	p = 0.51
BMI kg/m^2	28.2 ± 5.3	28.3 ± 4.4	p = 0.11
Gender			
Male	32 (26.66%)	46 (38.33%)	p = 0.12
Female	88 (73.33%)	74 (61.66%)	
Indication:			
LBP (Pain in Lower part of Back)	60 (50.00%)	60 (50.00%)	p = 0.57
Gonarthrosis	60 (50.00 %)	60 (50.00%)	
Synovitis in on gonarthrosis	6 (10.00%)	2 (3.3%)	p = 0.3
Stage of gonarthrosis			
Stage 1	0 (0.00%)	4 (6.67 %)	p = 0.12
Stage 2	52 (86.67%)	40 (66.67%)	
Stage 3	8 (13.3%)	16 (26.67%)	
The degree of functional impairment on gonarthrosis			
0	2 (3.33%)	6 (10.00%)	p = 0.54
1	34 (56.67%)	30 (50.00%)	
2	24 (40.00%)	22 (36.67%)	
3	0 (0.00%)	2 (3.33%)	
Type of treatment of LBP			
Acute	6 (10.00%)	10 (16.67%)	p = 0.54
Chronic	54 (90.00%)	50 (83.33%)	

Table 1: *Baseline characteristics of the patients.*

A total of 238 patients completed the study. Two patients withdrew from the study due to the reasons not related to the test drugs. According to the results obtained during statistical processing, significant differences in age, body mass index (BMI), gonarthrosis stage, and disease period, disease manifestation according to VAS in mm, evaluated by a physician and a patient and evaluation of pain at rest and in movement according to VAS in mm were not reported for the groups of Ketorolac and Ketoprofen (Table 2).

Statistically significant dynamics of pain intensity according to VAS both in the movement and at rest and positive evaluation of patient's health condition according to a physician and patient was reported in both groups of patients ($p < 0.05$) during the comparative evaluation of the efficacy of the drugs for topical use Ketorolac gel and Ketoprofen gel in patients with gonarthrosis and primary LBP (Tables 2, 3).

Test parameters	Before treatment	After treatment	Difference of mean
	Ketorolac, n = 59 (Mean ± SD)		
Pain at rest according to VAS, mm	53.76 ± 9.13	30.03 ± 18.14	23.73
Pain in motion according to VAS, mm	68.45 ± 9.45	39.76 ± 19.87	28.69*
Patient's health condition according to patient, VAS, mm	53.10 ± 15.78	69.31 ± 19.73	16.21
Patient's health condition according to physician, VAS, mm	59.55 ± 18.70	75.31 ± 18.15	15.76
	Ketoprofen, n = 60 (Mean ± SD)		
Pain at rest according to VAS, mm	52.40 ± 10.77	37.67 ± 13.98	14.73
Pain in motion according to VAS, mm	65.87 ± 13.08	49.13 ± 15.66	16.74
Patient's health condition according to patient, VAS, mm	51.27 ± 20.66	62.83 ± 15.93	11.56
Patient's health condition according to physician, VAS, mm	65.23 ± 16.40	73.33 ± 15.72	8.1

Table 2: *Dynamics of treatment efficacy parameters in group of patients with gonarthrosis (n = 119).*

**p =< 0.05, significant between the groups of Ketorolac vs Ketoprofen, for the same parameter*

Parameters	Before treatment	After treatment	Difference of mean[#]
	Ketorolac, n = 59 (Mean ± SD)		
Pain at rest according to VAS, mm	49.23 ± 23.48	34.43 ± 15.88	14.8
Pain in motion according to VAS, mm	66.60 ± 8.69	33.37 ± 21.38	33.23
Patient's health condition according to patient, VAS, mm	60.50 ± 14.00	76.80 ± 18.01	16.3
Patient's health condition according to physician, VAS, mm	71.57 ± 14.10	85.07 ± 16.34	13.5
	Ketoprofen, n = 60 (Mean ± SD)		
Pain at rest according to VAS, mm	40.83 ± 16.47	30.28 ± 15.32	10.55
Pain in motion according to VAS, mm	64.28 ± 8.60	34.86 ± 21.00	29.42
Patient's health condition according to patient, VAS, mm	59.03 ± 13.17	75.76 ± 18.91	16.73
Patient's health condition according to physician, VAS, mm	71.52 ± 12.94	85.45 ± 13.86	13.93

Table 3: *Dynamics of treatment efficacy parameters in group of patients with LBP (n = 119).*

[#]p values not significant between the groups of Ketorolac vs Ketoprofen, for the same parameter

Within the Ketorolac group, the change in VAS at rest was 23.73 mm and 14.8 mm for pain at rest and 28.69 mm and 33.37 mm for pain at motion in gonarthrosis and low back pain respectively, showing an improvement after treatment as compared to baseline. Similarly with Ketoprofen the change in VAS observed was 14.73 mm and 10.55 mm for pain at rest and 16.74 mm and 29.42 mm for pain at motion in gonarthrosis and low back pain respectively, showing an improvement after treatment as compared to baseline. This indicates that the improvement in pain at motion was significantly better with Ketorolac tromethamine gel as compared to Ketoprofen gel in gonarthrosis. No statistically significant differences in other efficacy parameters were reported between the groups of Ketorolac and Ketoprofen (Table 2).

According to opinion of physician, "Significant improvement" and "Improvement" has been shown in 95% cases in the groups of patients with pain in lower part of back and gonarthrosis in "Ketorolac" group as compared to 82% in "Ketoprofen" group, difference is statistically reliable (p = 0.001). Adherence to treatment mode in both groups of therapy corresponds to 100%.

In course of evaluation of tolerance of conducted therapy by the drug Ketorolac, according to opinion of doctor, "Significant improvement" and "Improvement" has been shown in 95% cases in the groups of patients with pain in lower part of back and gonarthrosis as compared to 82% in "Ketoprofen" group, difference is statistically reliable (p = 0.001). In course of evaluation of tolerance of conducted therapy by patients, evaluation "Excellent" and "Good" has been noted in 98% patients in the patients of "Ketorolac" group, while in "Ketoprofen" group – in 73%, difference is statistically reliable (p = 0.0003).

Safety and Tolerability Analysis

Both drugs - Ketorolac gel and Ketoprofen gel - demonstrated similar favorable safety profile for patients with LBP and gonarthrosis. Totally 2 mild adverse effects were reported in the test groups (application site dermatitis) which did not require the drug withdrawal.

Details of frequency of side effects in both study arms is summarized in table 4.

Index	"Ketorolac" group	"Ketoprofen" group
No side effect	118 (98.31%)	119 (99.16%)
Presence of side effect	2 (1.69%)	1 (0.84%)
Fisher exact, one-tailed p = .5		

Table 4: *Evaluation of frequency of side effects.*

Two side effects were noted in the group of patients taking Ketorolac: Dermatitis at the site of drug application, mild degree of severity, relation with intake of the drug was evaluated as "Probable", did not require additional therapy or withdrawal of drug.

Epigastric pain while using drug Ketorolac, mild degree of severity, relation with intake of the drug was evaluated as "Suspicious", Omeprazole 20 mg twice in a day -7 days was added to the therapy, outcome- recovery.

In course of studies 1 side effect has been recorded in the group of patients taking Ketoprofen: Dermatitis at the site of gel application, relation with taking the drug was evaluated as "Probable", does not require additional therapy or withdrawal of drug.

Discussion

Our study compared topical Ketorolac and topical Ketoprofen in patients with gonarthrosis and low back pain. Topical Ketorolac and topical Ketoprofen showed reduction in VAS from baseline in patients with gonarthrosis and low back pain on comparison of efficacy indices in the patients with pain syndrome in the lower part of back as per VAS scale, the change in VAS score was more with Ketorolac vs Ketoprofen. On comparison of efficacy indices in the patients with gonarthrosis, the effectiveness of relief of pain syndrome in Ketorolac group significantly exceeds that of Ketoprofen group, with respect to Pain in motion. Both agents were well tolerated and "Excellent" and "Good" was noted in 98% patients in "Ketorolac" group, while 73% in Ketoprofen group (p = 0.0003).

Limited data is available on use of topical ketorolac gel. In the study by Diebschlag W., et al. (1990), topical ketorolac tromethamine gel was studied in the treatment of ankle sprain [17]. Reductions in VAS pain at rest were more marked in the ketorolac group with a significant difference on day 4 as against other groups (placebo and Etofenamate). Reductions in VAS pain on movement were more for the ketorolac group at all visits. The differences between ketorolac and each of the other groups achieved statistical significance on days 4 and 8. However, this study was done in patients with ankle sprain, where as we evaluated ketorolac gel in patients with gonarthrosis or low back pain.

NSAIDs are the mainstay of management of musculoskeletal pain but oral formulations are frequently associated with systemic side effects in the form of gastrointestinal and cardiovascular adverse effects, and also limits their chronic use. In such a context topical NSAIDs such as ketorolac provide effective analgesia with limited systemic adverse effects, making them a suitable choice for use in acute and chronic musculoskeletal painful conditions.

Discussion

Our study compared topical Ketorolac and topical Ketoprofen in patients with gonarthrosis and low back pain. Topical Ketorolac and topical Ketoprofen showed reduction in VAS from baseline in patients with gonarthrosis and low back pain on comparison of efficacy indices in the patients with pain syndrome in the lower part of back as per VAS scale, the change in VAS score was more with Ketorolac vs Ketoprofen. On comparison of efficacy indices in the patients with gonarthrosis, the effectiveness of relief of pain syndrome in Ketorolac group significantly exceeds that of Ketoprofen group, with respect to Pain in motion. Both agents were well tolerated and "Excellent" and "Good" was noted in 98% patients in "Ketorolac" group, while 73% in Ketoprofen group ($p = 0.0003$).

Conclusion

Our study data shows that Ketorolac 2% gel for topical application has good clinical efficacy, evident analgesic effect, well tolerated which makes its administration in the treatment of musculoskeletal disease in outpatient setting.

Conflict of Interest

The clinical study was sponsored by Dr. Reddy's Laboratories Ltd., Hyderabad, India. N.A. Shostak received research funding. Amit Garg, Suhas Khandarkar and Shyam Akku are the employees of Dr. Reddy's Laboratories Ltd., Hyderabad, India.

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