

Efficacy and Safety of Nimesulide Transdermal Gel versus Diclofenac and Piroxicam Gel in Patients with Acute Musculoskeletal Condition

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ABSTRACT

In this single blind, randomized, comparative evaluation of nimesulide transdermal gel (Nimesulide Trans gel) versus diclofenac and piroxicam gel in acute musculoskeletal conditions, two hundred and seventy-six patients were analysed for assessing the efficacy and safety of these gels.

More number of patients got better relief in pain and inflammation parameters with nimesulide transdermal gel than the other two groups. The drug related side effects were low and not significant.

Key Words : Acute Musculoskeletal Condition - Transdermal gel

Musculoskeletal injuries are frequently incurred in normal daily activities, limiting activity because of pain & inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the management of these symptoms, for relief.

The expectation of limiting direct gastric irritation by using topical formulations is appealing. But the question of efficacy looms large. There have been sufficient number of studies of soft tissue conditions to demonstrate the superiority of topical NSAIDs over placebo and to suggest equivalent efficacy in comparison with some oral NSAIDs.

This study was performed to determine the comparative efficacy, tolerability and acceptability of topical applications of a relatively new formulation of nimesulide transdermal gel (1%w/w), with diclofenac gel (1%w/w) and piroxicam gel (0.5%w/w).

MATERIAL AND METHODS :

This was a single blind, multicentric, randomized, comparative trial conducted at LNJ Hospital, Delhi; K. G. Medical College, Lucknow and SMS Medical College, Jaipur.

The patients were divided into three groups receiving either nimesulide transdermal gel, piroxicam gel or diclofenac gel.

The patients were asked to rub the coded gels onto the affected part 3-4 times daily for a period of 8 days.

Patients (males and non-pregnant females) between 18 to 70 years of age suffering from acute musculoskeletal conditions were included in the study. Recent injuries sustained within 48 hours (not requiring surgical treatment) were included under "acute" category. Written informed consent was obtained prior to enrollment of patients in the study.

Patients with injuries requiring immobilization, orthopaedic or surgical intervention; those with a history of allergy to aspirin and/or other NSAIDs; those taking aspirin or other NSAIDs for 3 days prior to enrollment; those receiving systemic or local corticosteroids within 1 week of beginning of the study; those receiving any medication other than cold packs and elevation for this event; those with localized or generalized skin disease or having break in continuity of skin; patients with severe systemic disorders and carcinomas; pregnant and lactating mothers; female patients with child bearing potential unless under contraceptive, cover were excluded from the study.

The patients were evaluated before initiation of therapy and then at day 1, day 4 and day 8 of therapy for the following parameters.

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); swelling on a 4 point scale (0-absent, 1-mild, 2 moderate, 3-severe); tenderness on a 4 point scale (0-not tender, 1-tender, 2-wincing, 3-withdraw); and functional impairment on a 5 point scale (0-

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 trial drugs.

Global efficacy and tolerance of the treatment was judged both by the patients and physician at the end of treatment. Adverse effects if any were also recorded in the case report form.

The nonparametric data between groups was evaluated using Kruskal Wallis one-way analysis of variance. If there was evidence of a significant difference between the treatments, individual treatment group comparisons were made using Wilcoxon rank sum test. Within group analysis was done using Wilcoxon signed-rank test.

RESULTS:

A total of 300 patients were enrolled at all the three centers together. However, 24 patients were lost to follow up and only 276 patients were evaluable. A total of 99 patients received nimesulide transdermal gel, 80 received piroxicam gel, and 97 received diclofenac gel. The ratio of males to females in the study was 17:29 (102/174). The patients' demographics of all the three groups were comparable (Table 1).

Table 1: Patient Demographics

Parameters	Nimesulide Transdermal gel	Piroxicam gel	Diclofenac gel
Total no. of patients	99	80	97
Sex:			
Male	33	36	33
Female	66	44	64
Mean Age (years)	35.83±14.14	35.55±12.12	36±12.13

Table 2 represents the percentage of patients assessed for a particular parameter and Table. 3 represents the mean scores of efficacy parameters.

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 8 days there was no significant change in the paracetamol intake in all the 3 groups.

Table 3 Mean scores of Efficacy Parameters

Day Characteristics	Nimesulide Transdermal gel (n = 99)				Piroxicam gel (n = 80)				Diclofenac gel (n = 97)			
	0	1	4	8	0	1	4	8	0	1	4	8
Pain Intensity on VAS (cm)	4.15	5.25	6.2	7.12	4.07	5.1	5.9	6.6	4.6	5.3	5.7	6.1
Pain at Rest	1.5	1.2	0.7	0.3	1.3	1.1	0.7	0.4	1.4	1.2	0.8	0.4
Pain on passive Motion	1.8	1.5	0.8	0.4 ^{*a}	1.5	1.3	0.8	0.6	1.7	1.4	0.5	0.7
Pain on palpation	1.5	1.2	0.8	0.4 ^{a,***a}	1.5	1.3	0.9	0.6	1.4	1.2	1.8	0.6
Pain on Isometric Contraction	1.5	1.2	0.8	0.5	1.3	1.2	0.8	0.5	1.4	1.2	0.8	0.6
Swelling	0.8	0.7	0.3 ^{*b}	0.1	1.02	0.9	0.6	0.3	0.8	0.7	0.4 ^{*b}	0.2
Tenderness	1.3	1.04	0.6	0.3	1.3	1.1	0.7	0.5	1.2	1.1	0.7	0.4
Functional Impairment	1.6	1.3	0.8	0.5	1.5	1.3	0.8	0.6	1.6	1.3	0.9	0.6

*a p<0.1 (Nimesulide Vs Diclofenac) *b p<0.01 (Nimesulide Vs Piroxicam)

**a p<0.05 (Nimesulide Vs Piroxicam) **b p<0.05 (Diclofenac vs Piroxicam)

The onset of pain relief was normally observed within 15-60 minutes. In some cases the onset of pain relief was quite delayed, but there was not much difference between the groups.

The between group analysis showed that treatment with nimesulide transdermal gel was significantly more effective than diclofenac gel and clinically better than the piroxicam gel. The pain intensity on a 10cm visual analogue scale was best ever in 19.73% of the patients in nimesulide transdermal gel group, 11.76% with piroxicam gel and 1.47% with diclofenac gel group at the end of therapy. The pain intensity mean score of 7.12cm (when assessed on 0-10cm VAS) for nimesulide transdermal gel was statistically more significant ($p < 0.01$) than diclofenac gel where the mean score was 6.1cm.

At day 8, there were 68.69% patients with no pain at rest in the nimesulide transdermal gel group, 60% in the piroxicam group and 61.86% in the diclofenac gel group. No statistically significance was seen between groups in their mean scores.

Pain at passive motion was absent in 61.22% patients in the nimesulide transdermal gel group, 47.5% patients in piroxicam group and 39.18% in diclofenac group. Nimesulide transdermal gel showed significantly better improvement than diclofenac gel ($p < 0.01$) on day 8 for mean scores.

TABLE 2: Assessment of patients For the treatment given for various parameters*

Day Characteristics	Nimesulide Transdermal gel (n = 99)				Piroxicam gel (n = 80)				Diclofenac gel (n = 97)			
	0	1	4	8	0	1	4	8	0	1	4	8
Pain Intensity on VAS (cm)												
0	1.41	1.41	0.00	1.41	1.96	1.96	0.00	0.00	0.00	0.00	0.00	0.00
1	1.41	0.00	0.00	0.00	5.88	3.92	5.88	1.96	2.94	0.00	0.00	0.00
2	8.45	0.00	4.23	0.00	7.84	0.00	0.00	5.88	8.82	1.47	0.00	4.41
3	23.94	19.72	5.63	4.23	15.69	7.84	0.00	1.96	14.71	5.88	7.35	4.41
4	23.94	9.86	8.45	7.04	19.61	15.69	15.69	7.84	22.06	17.65	13.24	10.29
5	25.35	22.54	15.49	12.68	37.25	27.45	13.73	1.96	20.59	26.47	22.06	11.76
6	8.45	28.17	16.90	15.49	9.80	27.45	23.53	27.45	19.12	33.82	30.88	27.94
7	5.63	4.23	19.72	11.27	0.00	3.92	21.57	17.65	5.88	7.35	13.24	19.12
8	0.00	11.27	19.72	14.08	1.96	11.76	15.69	13.73	4.41	5.88	8.82	13.24
9	1.41	2.82	9.86	14.08	0.00	0.00	3.92	9.80	1.47	1.47	2.94	7.35
10	0.00	0.00	0.00	19.72	0.00	0.00	0.00	11.76	0.00	0.00	1.47	1.47
Pain at rest												
Absent (0)	7.07	11.11	35.35	68.69	5.00	8.75	26.25	60.00	6.19	11.34	29.90	61.86
Mild (1)	33.33	49.49	59.60	30.30	52.50	63.75	68.75	35.00	47.42	54.64	56.70	35.05
Moderate (2)	54.55	38.38	4.04	1.01	41.25	27.50	5.00	5.00	46.39	34.02	12.37	1.03
Severe (3)	5.05	1.01	1.01	0.00	1.25	0.00	0.00	0.00	0.00	0.00	1.03	2.06
Pain on Passive Movement												
Absent (0)	2.04	3.06	29.59	61.22	3.75	5.00	23.75	47.50	2.06	2.06	16.49	39.18
Mild (1)	31.63	47.96	56.12	30.61	40.00	60.00	63.75	46.25	31.96	52.58	67.01	51.55
Moderate (2)	50.00	40.82	13.27	8.16	52.50	35.00	12.50	6.25	55.67	43.30	16.49	9.28
Severe (3)	16.33	8.16	1.02	0.00	3.75	0.00	0.00	0.00	10.31	2.06	0.00	0.00
Pain on palpation												
Absent (0)	12.37	20.62	32.99	60.82	3.75	6.25	18.75	42.50	6.19	9.28	24.74	38.14
Mild (1)	30.93	31.96	53.61	34.02	38.75	55.00	67.50	53.75	43.30	57.73	62.89	57.73
Moderate (2)	47.42	42.27	11.34	4.12	52.50	37.50	13.75	3.75	46.39	31.96	11.34	3.09
Severe (3)	9.26	5.15	2.06	1.03	5.00	1.25	0.00	0.00	4.12	1.03	1.03	1.03
Pain at Isometric Contraction												
Absent (0)	5.05	12.12	31.31	52.53	10.13	15.19	27.85	49.37	6.19	10.31	30.93	43.30
Mild (1)	44.44	52.53	54.55	41.41	49.37	49.37	63.29	45.57	44.33	59.79	52.58	52.58
Moderate (2)	43.43	30.30	14.14	6.06	32.91	31.65	5.06	2.53	44.33	28.87	16.49	4.12
Severe (3)	7.07	5.05	0.00	0.00	7.59	3.80	3.80	2.53	5.15	1.03	0.00	0.00
Swelling												

Absent (0)	37.37	42.42	66.67	86.67	29.11	32.91	43.04	69.62	39.18	45.36	59.79	72.16
Mild (1)	42.42	45.45	28.28	13.13	40.51	43.04	51.90	26.58	39.18	38.14	35.05	26.80
Moderate (2)	18.18	11.11	5.05	0.00	29.11	24.05	5.06	3.80	21.65	16.49	5.15	1.03
Severe (3)	2.02	1.01	0.00	0.00	1.27	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tenderness												
Not Tender (0)	10.10	17.17	41.41	65.66	5.06	8.86	27.85	49.37	9.28	9.28	29.90	54.64
Tender (1)	48.48	64.65	53.54	31.31	56.96	72.15	65.82	48.10	55.67	7.10	62.89	41.24
Wincing (2)	35.35	15.15	4.04	3.03	34.18	18.99	6.33	2.53	31.96	19.59	7.22	4.12
Withdrew (3)	6.06	3.03	1.01	0.00	3.80	0.00	0.00	0.00	3.09	1.03	0.00	0.00
Functional Impairment												
None (0)	7.22	16.49	38.14	58.76	10.00	13.75	31.25	47.50	6.19	7.22	22.68	41.24
Mild (1)	38.14	38.14	45.36	32.99	38.75	46.25	55.00	45.00	39.18	54.64	58.76	51.55
Moderate (2)	42.27	37.11	14.43	6.19	43.75	33.75	10.00	2.50	39.18	32.99	17.53	6.19
Marked (3)	9.28	7.22	2.06	2.06	6.25	5.00	3.75	5.00	14.43	5.15	1.03	1.03
Severe (4)	3.09	1.03	0.00	0.00	1.25	1.25	0.00	0.00	1.03	0.00	0.00	0.00

* All values are given as percentage of patients approximated to two decimal places.

Pain on palpation was also found to be absent in 60.83% in nimesulide transdermal gel group, 42.5% in piroxicam and 38.14% in diclofenac group at the end of therapy. Nimesulide transdermal gel showed significantly better improvement than piroxicam ($p < 0.05$) and diclofenac gel ($p < 0.01$) in *pain* on palpation mean scores.

Pain at isometric contraction also was absent in more number of patients in nimesulide transdermal gel group : 52.53%, 49.37% and 43.3% in nimesulide, piroxicam and diclofenac group respectively. However, no statistical significance was seen between all the three groups.

Absence in swelling was observed in more number of patients treated with nimesulide transdermal gel (86.87%) followed by diclofenac gel (72.16%) and piroxicam gel (69.62%). On day 4, nimesulide transdermal gel was statistically better ($p < 0.01$) in reducing the swelling than piroxicam gel. Diclofenac gel rated better ($p < 0.05$) in this parameter as compared to piroxicam gel.

Clinically, tenderness was absent in 65.66% patients in nimesulide, 49.37% in piroxicam gel and 54.64% in diclofenac gel group. Functional impairment was absent in 58.76%, 47.5% and 41.24% patients on nimesulide, piroxicam and diclofenac gel groups respectively. There was statistically non-significant difference between the three groups in the mean tenderness and functional impairment at all assessment points.

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

Global efficacy as judged by both the patient and physician indicated that nimesulide transdermal gel is more effective than diclofenac gel and comparable to piroxicam gel.

DISCUSSION:

A successful topical NSAID requires not only efficacy at the target site but the ability to reach that site, which may involve delivery via the systemic circulation and direct penetration. The clinical effect achieved may also reduce the requirement of oral NSAID therapy decreasing the side effects.

The skin layers through which any drug must be transported are the stratum corneum, viable epidermis, the basement membrane and the dermis (Hadgraft-1989). Absorption into the systemic circulation or penetration into deeper tissues occurs from this point (Singh 1994).

Studies in which various NSAIDs have been applied directly to rat dermis, with the major epidermal barrier removed, show almost equal penetration between drugs to deeper tissues, indicating that most of the variability between drugs in terms of transcutaneous absorption relates to their relative ability to negotiate

the superficial layers.

The use of topical NSAIDs have recently become very popular. These preparations are claimed to be devoid of the dose limiting toxicity of systematic NSAIDs (Somervelle 1986).

Nimesulide has good analgesic and anti-inflammatory activity (Davis 1994). Many studies of this drug have reported good results in terms of decreasing pain and improved functions in musculoskeletal conditions by systemic routes.

In previous studies, conducted by Gupta et al, (1996) in albino rats, topical nimesulide transdermal gel possessed higher anti-inflammatory activity than that of diclofenac or piroxicam gels in various experimental models.

Sen Gupta et al (1998) also suggested in studies conducted on mice that the transdermal formulation of nimesulide provided significant analgesic activity when applied topically.

The superior analgesic activity of nimesulide transdermal gel formulation, correlating with its, pharmacokinetic profile, indicates that the topical route of administration may be a safe and effective alternative to other routes (Sen Gupta 1998). Dhaon e.L al (1998) have also reported good results in terms of decreasing pain and improved functions in musculoskeletal conditions after topical application of nimesulide transdermal gel in their earlier study.

Clinical trials are most favourable in supporting the use of local preparations in acute, self-limiting soft tissue injuries. In our study, all three groups reported improvement in various parameters at the end of therapy. Clinically more number of patients got relief in pain and inflammation parameters with nimesulide transdermal gel than the other two groups.

Nimesulide transdermal gel was statistically more significant in reducing the mean scores of pain intensity on VAS, pain at passive motion, pain on palpation, absence of swelling when compared with diclofenac and piroxicam gels.

More number of patients rated nimesulide transdermal gel as very good in efficacy and tolerance as compared to other two groups. The incidence of drug related side effects although low, was highest with piroxicam followed by diclofenac and nimesulide transdermal gel.

Most of the anti-inflammatory drugs have a rather low solubility. Nimesulide transdermal gel is a novel hydroalcoholic microcarrier based drug delivery system with penetration enhancer. In our study, this may be the possible cause of superior efficacy of nimesulide transdermal gel over piroxicam and diclofenac gel on local application.

The efficacy and tolerability of nimesulide transdermal gel in treatment of acute musculoskeletal conditions was superior to that of diclofenac and piroxicam gel. Nimesulide transdermal gel would be a more useful and tolerable addition in the range of established treatments for acute musculoskeletal injuries in orthopaedic practice.

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