ORIGINAL ARTICLE

A NOVEL QUICK PENETRATING SOLUTION OF DICLOFENAC (TOPICAL) FOR MANAGEMENT OF ACUTE MUSCULOSKELETAL PAIN

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ABSTRACT

BACKGROUND: Inadequate penetration of topical formulation compels the use of oral NSAIDs for the management of musculoskeletal pain, despite the incidences of systemic adverse events. Dynapar QPS (Quick Penetrating Solution) is a novel topical solution of diclofenac diethylamine (4.64%) with increased penetration. The present study was designed to compare the efficacy and safety of Dynapar QPS with diclofenac gel in acute musculoskeletal pain. **MATERIALS AND METHODS:** 230 Patients suffering from moderate to severe acute musculoskeletal pain (acute low backache or pain following trauma to muscles, tendons, ligaments or joints) were randomized to receive either Dynapar QPS or diclofenac gel. Study medications were applied three times daily for 7 days. Time to onset of analgesia and intensity of pain on visual analogue scale were measured at 3rd and 7th day of application. Other parameters like pain at rest and during movement; degree of functional impairment and adverse events; global assessment were also evaluated. **RESULTS AND DISCUSSION:** Time to onset of analgesia was significantly shorter with QPS as compared to gel on day 3 (21.4±9.70 vs 33.8±17.72 min) and on day 7 (18.4±7.77 vs 31.0±18.08) ($P<0.0001$ for day 3 and day 7). 80% of the patients with Dynapar QPS and 55.7% patients with gel ($P<0.0001$) reported pain reduction by at least 50%. Dynapar QPS was also found to be better in secondary end points. No adverse events were reported in either arm in the study. **CONCLUSION**: Dynapar QPS provides superior efficacy compared to diclofenac gel without compromising safety in management of acute musculoskeletal pain.

Keywords: Diclofenac gel, diclofenac topical solution, musculoskeletal pain, topical non-steroidal anti-inflammatory drugs, quick penetrating solution

INTRODUCTION

Musculoskeletal pain is one of the common condition for which people seek medical care. Virtually all adults must have experienced one or more brief episodes of musculoskeletal pain associated with injury or overuse.[1]Non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone for musculoskeletal pain management.[2] Oral NSAIDs carry significant dose-related risks of cardiovascular, renal, hematological and other systemic adverse events.

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Use of NSAID approximately doubles the risk of acute renal failure, and a linear dose-response relationship has been established between use of oral NSAIDs and upper GI bleeding.[3] Around 40% of hospital admissions with upper gastrointestinal bleeding and 40% of associated deaths in older people are related to NSAID use.[4] Topical diclofenac can avoid adverse events associated with oral diclofenac. Topical diclofenac may limit its systemic exposure by acting locally with less systemic distribution.[5] Hence, topical diclofenac is recommended over oral diclofenac by various guidelines.[6,8] Currently available topical formulations of diclofenac include creams, gels or aerosol sprays. Topically applied drugs have to cross the barrier of stratum corneum to reach to the underlying tissue.[9] It is reported that only 10% of diclofenac from the topically applied gel is biologically available and the penetration depth is merely 3-4 mm.[10] The failure of currently available topical formulations in providing effective pain relief mandates the use oral NSAIDs.[11] Dynapar QPS is a novel Quick Penetrating Solution of

diclofenac which is manufactured using non aqueous and non volatile solvents which help increasing penetration of the drug across the skin. Increased penetration of diclofenac from Dynapar QPS can provide better efficacy compared to conventional diclofenac gel. The present study was designed to evaluate the efficacy and safety of Dynapar QPS in comparison to diclofenac gel in patients suffering from acute musculoskeletal pain.

MATERIALS AND METHODS

This prospective, randomized, two arm, open label, phase III clinical study was conducted at 5 different hospitals across India. The study protocol was approved by office of Drug Controller General of India and Ethics Committees. The study was registered to clinical trial registry-India (CTRI) prior to initiation of the study (CTRI Registration No: CTRI/2010/091/003050). The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India, and the ethical standards laid down in declaration of Helsinki 1964 and its later amendments; and Ethical guidelines for biomedical research on human participants issued by Indian Council of Medical Research (2006), New Delhi. Written informed consent was taken from each patient before screening for trial. Men and non-pregnant women, aged 18- 70 years, with at least moderate pain [visual analogue scale (VAS) $\geq$ 4] from acute musculoskeletal pain for not more than 2 days due to acute low back ache (non- specific) or pain and inflammation following trauma to muscle, tendons, ligaments or joints (due to strains, sprains, musculoskeletal stress, soft tissue injuries or blunt sports injuries) were enrolled in the study from March 2011 to December 2012. Patients were excluded if they had known contraindications to NSAIDs; hypersensitivity to NSAIDs or any other component of study medications; open injury with broken skin; been using oral NSAIDs or medicines that may interfere with the study medications; concomitant skin disease at the application site. Enrolled subjects were randomized to receive either QPS containing diclofenac diethylamine 4.64 % w/v (Dynapar QPS, Troikaa Pharmaceuticals Ltd, Ahemdabad, India) or topical gel containing diclofenac diethylamine 1.16 % w/w (Voveran Emulgel, Novartis India Ltd.). Randomization was performed using computer generated simple randomization sheet with equal distribution of the patients in both the groups. Patients were instructed to apply the medication at the site of pain 4 times a day for 7 days. Intensity of pain at affected area was measured using 10 point VAS (where 0 indicates no pain and 10 indicates worst possible pain) at baseline, day 3 and day 7 of the study. Severity of pain at rest and during movement was assessed using 4 point verbal rating scale (0- absent, 1- mild, 2- moderate and 3- severe) at baseline and day 7. Patients were instructed to record time to onset of analgesia at day 3 and day 7 of application. Degree of functional impairment was assessed using 5 point verbal rating scale (0- none, 1-mild, 2-moderate, 3-marked, 4- severe) at baseline and day 7. Each patient was enquired about the adverse events experienced during study period. At the end of the study (day 7), both investigator and patients rated their global assessment of treatment based on safety and efficacy of study drugs. Time to onset of analgesia, improvement in pain intensity and proportion of patients having at least 50% reduction in pain at day 7 were primary efficacy endpoints. Secondary efficacy endpoints included pain at rest and during movement, degree of functional impairment and global assessment by physicians and patients. Sample size was calculated using software, PS Power and Sample Size Calculations Program (version 3) based on the study comparing topical ketoprofen patch with diclofenac gel in soft tissue injury.[12] To measure the critically evaluable difference of 1 point on VAS (of 0 to 10 where 0 is no pain and 10 is worst possible pain) with standard deviation (SD) of 2.3, the sample size was calculated at 90% power and at 5% level of significance using two sided test. Based on sample size calculation, 112 patients were required in each group. Considering a drop out rate of 5 %, 117 patients were required in each treatment group. The data are presented in the form of mean ± SD for continuous variables and in proportions for categorical variables. Appropriate parametric or non parametric tests have been used depending on the distribution of data. $P< 0.05$ is considered significant. All statistical analyses were performed using software, Statistical Analysis System (SAS), version no. 1.9.

RESULTS

Out of these 250 patients screened, 230 were found to be eligible for enrolment. The enrolled patients were equally distributed in both the groups. Demographic data showed equal distribution of patients in both the arms in terms of age, sex, height, weight and baseline pain intensity. Distribution pattern of patients with different aetiology of acute musculoskeletal pain was similar in both the groups (Table 2).

Time to onset of analgesia at day 3 and day 7 was significantly shorter with patients using Dynapar QPS compared to diclofenac gel (Table 1). Both the

drugs showed improvement in pain intensity from the baseline. However, patients treated with Dynapar QPS experienced significant improvement in pain intensity as compared to diclofenac gel on day 3 ($p < 0.0001$) and day 7 ($p < 0.0001$) (Table 3). Proportion of patients having at least 50% pain reduction was significantly higher ($P < 0.0001$) with Dynapar QPS [93 patients (80.86%)] compared to diclofenac gel [64 patients (55.65%)] (Table 4).

Results of the secondary endpoints including pain intensity at rest and movement; degree of functional improvement and global assessments are provided in Table 5. Pain intensity at rest and during movement was reduced by both the study medications. At the end of the study, pain intensity at rest was reported as absent by 86 patients (74.78%) in Dynapar QPS group; whereas 63 patients (54.78 %) reported absence of pain with diclofenac gel ($p = 0.05$). Similarly pain intensity on movement was mild or absent in 96 patients (83.48%) with Dynapar QPS compared to 77 patients (66.96%) with diclofenac gel ($p < 0.001$). Patient and physician's global assessment showed favourable trends toward Dynapar QPS over diclofenac gel ($p < 0.001$). The Dynapar QPS and diclofenac gel were equally well tolerated throughout the study period. No cases of any expected and unexpected adverse events were observed or reported during study.

Table 1: Time to Onset of analgesia at 3rd and 7th day of application

Days	Time to onset of analgesia (Min)		P Value
	Dynapar QPS (N = 115)	Diclofenac Gel (N = 115)	
Day 3	21.4 ± 9.70	33.8 ± 17.72	<0.0001
Day 7	18.4 ± 7.77	31.0 ± 18.08	<0.0001

N = number of subject in each treatment group. Values are expressed in Mean ± SD. Data were analyzed by unpaired't' test

Table 2: Demography and baseline characteristics of the patients

Characteristic	Dynapar QPS (N = 115)	Diclofenac Gel (N = 115)	*P* value
Age (Year)	42.5 ± 12.39	43.4 ± 12.23	0.5804*
Gender (Male/Female)	52/63	47/68	0.6099**
Height (cm)	160.0 ± 7.08	160.7 ± 7.59	0.4710*
Weight (Kg)	64.6 ± 10.47	65.1 ± 12.19	0.7392*
Baseline pain intensity (VAS)	6.3 ± 1.23	6.4 ± 1.14	0.2329*
Diagnosis			
Low backache	28	29	0.7638**
Strain	19	27	
Sprain	49	40	
Musculoskeletal stress	4	3	
Soft tissue injury	3	6	
Blunt sports injury	9	7	
Others	3	3	

Values are expressed in Mean ± SD for age, height, weight and baseline pain intensity; absolute number for gender and diagnosis. N = number of patients in treatment group. *Data were analyzed by unpaired 't' test **Data were analyzed by Chi square test

Table 3: Improvement in pain intensity from baseline at 3rd and 7th day of application

Days	Improvement in pain intensity (VAS)		P Value
	Dynapar QPS (N = 115)	Diclofenac Gel (N = 115)	
Day 3	2.1 ± 0.92	1.6 ± 0.86	<0.0001
Day 7	4.1 ± 1.32	3.4 ± 1.31	<0.0001

N = number of subject in each treatment group. Values are expressed in Mean ± SD. Data were analyzed by unpaired 't' test

Table 4: Proportion of patients having at least 50% reduction in pain at the end of the study

Pain reduced by at least 50%	Dynapar QPS (N = 115)	Diclofenac Gel (N = 115)	P Value
Yes	93 (80.86%)	64 (55.65%)	<0.0001
No	22 (19.13%)	51 (44.34%)	

N = number of subject in each treatment group. Values are expressed in absolute number and percentage. Data were analyzed by Chi square test

Table 5: Results of secondary efficacy parameters

Pain intensity at Rest (Baseline)					
Treatment	**Absent**	**Mild**	**Moderate**	**Severe**	**P Value**
Dynapar QPS (N = 115)	15	60	39	1	0.837
Diclofenac Gel (N = 115)	17	54	42	2	
Pain intensity at Rest (Day 7)					
Treatment	**Absent**	**Mild**	**Moderate**	**Severe**	**P Value**
Dynapar QPS (N = 115)	86	27	2	0	0.005
Diclofenac Gel (N = 115)	63	48	4	0	
Pain intensity on movement (Baseline)					
Treatment	**Absent**	**Mild**	**Moderate**	**Severe**	**P Value**
Dynapar QPS (N = 115)	0	2	81	32	0.828
Diclofenac Gel (N = 115)	0	2	86	27	
Pain intensity on movement (Day 7)					
Treatment	**Absent**	**Mild**	**Moderate**	**Severe**	**P Value**
Dynapar QPS (N = 115)	10	86	17	2	< 0.001
Diclofenac Gel (N = 115)	1	76	36	2	
Degree of functional impairment (baseline)						
Treatment	**None**	**Mild**	**Moderate**	**Marked**	**Severe**	**P Value**
Dynapar QPS (N = 115)	4	14	70	24	4	0.943
Diclofenac Gel (N = 115)	3	16	73	20	3	
Degree of functional impairment (Day 7)						
Treatment	**None**	**Mild**	**Moderate**	**Marked**	**Severe**	**P Value**
Dynapar QPS (N = 115)	47	57	8	3	0	< 0.001
Diclofenac Gel (N = 115)	20	66	25	4	0	
Physician's global assessment					
Treatment	**Excellent**	**Good**	**Fair**	**Poor**	**P Value**
Dynapar QPS (N = 115)	44	54	14	3	< 0.001
Diclofenac Gel (N = 115)	17	44	49	5	
Patient's global assessment					
Treatment	**Excellent**	**Good**	**Fair**	**Poor**	**P Value**
Dynapar QPS (N = 115)	39	53	19	4	< 0.001
Diclofenac Gel (N = 115)	6	42	60	7	

N = number of subject in each treatment group. Values are expressed in absolute numbers for each category. Data were analyzed by Fisher's exact test

DISCUSSION

Lack of effectiveness of currently available topical formulations of NSAIDs compels the use of oral NSAIDs for the management of musculoskeletal pain, despite of their side effects. Dynapar QPS is a novel formulation which increases the penetration of diclofenac through stratum corneum. This study was conducted to evaluate the efficacy and safety of Dynapar QPS comparison to the conventional topical NSAID formulation in the management of acute musculoskeletal conditions. Diclofenac emulgel containing diclofenac sodium (1% w/w) is one of the most commonly used topical NSAID formulations, in India; hence it was selected as a

comparator in this study. Musculoskeletal pain is a broad term including wide variety of conditions. Patients with musculoskeletal conditions like low back pain, strain, musculoskeletal stress, soft tissue injuries and blunt injuries were included in this study. Distribution of the patients with different conditions was similar in both the groups. In this study, Dynapar QPS was found to have earlier onset of action compared to diclofenac gel. Improvement in pain intensity was also better with Dynapar QPS compared to diclofenac gel. It is well established that effectiveness of topical preparation depends on the amount of drug reaching to the site of action.[9] Currently available diclofenac topical gels are aqueous in nature and penetration of diclofenac through the topical gel is not sufficient to reduce the pain effectively. Non aqueous solvents and higher concentration of diclofenac in Dynapar QPS promote higher tissue penetration of diclofenac.[13] The results obtained in this study are in line with other the studies showing efficacy of topical formulation of diclofenac with improved penetration.[14,15] In this study, no adverse events were recorded with either study group. Safety results suggested that, while improving the efficacy of diclofenac through QPS, safety of the patients was not vitiated. Earlier studies have shown that the topical formulations of diclofenac with higher penetration are safe and do not have significant systemic side effects.[16,17] This can be explained by the fact that increasing penetration of diclofenac in the local tissues does not lead to significant increase in systemic exposure. It has been reported that after repeated administration (three times a day for 7 days) of a topical formulation of diclofenac, the concentration of diclofenac was 3.25 times higher in the subcutaneous adipose tissue and 2 times higher in skeletal muscle tissue compared with oral dosing, whereas relative plasma bioavailability was 50-fold lower.[13] Similar results have also been observed for a topical diclofenac formulated using penetration enhancer.[18] In this study, the Dynapar QPS showed quick onset of action, better improvement in pain intensity and functional impairment and was well tolerated in the wide variety of musculoskeletal pain.

CONCLUSION

Dynapar QPS, a novel formulation of topical diclofenac, provides superior efficacy compared to topical diclofenac gel without compromising the safety in the management of acute musculoskeletal pain. Improved pain relief with Dynapar QPS may help in minimizing the NSAID induced side effects by reducing the need of oral NSAIDs however this needs to be confirmed in further study.

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