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Original Article

Orthopaedics Section

Efficacy and Safety of Naproxen Gel in Musculoskeletal Pain Management: A Prospective Cohort Study

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ABSTRACT

Introduction: Naproxen is effective for various musculoskeletal conditions and has a longer half-life, making it a favourable choice for sustained relief. Additionally, there is a potential unmet need for guidelines on the usage of topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the Asia-Pacific region. A study on naproxen 10% gel aims to address this need and increase awareness of its therapeutic potential in the region.

Aim: To assess the efficacy and safety of naproxen 10% gel in relieving pain associated with lower back, knee, cervical, synovitis, bursitis, muscle sprain, and tendinitis.

Materials and Methods: This prospective, cohort, observational, open-label, single-arm, multicentric study was conducted at 458 centres in India, including Ahmedabad, Bengaluru, Chandigarh, Chennai, Delhi, Guwahati, Hyderabad, Indore, Jaipur, Kolkata, Lucknow, Meerut, Mumbai, Patna, and Pune, between February 2023 and May 2023. The data was collected from outpatient settings/clinics of orthopaedicians and clinicians who have been prescribing topical naproxen 10% gel to their patients. The study included patients aged 18 to 60 years of either sex who were suffering from back pain, muscle pain, sprains, frozen shoulder, arthritis, acute low back ache (non-specific), or pain. The data was captured during the scheduled follow-up visits planned by the treating clinician, with data recorded at 3, 5, 10, and 15 days. At the baseline visit, demographic details (age, sex, weight, height, body mass index, and symptoms), Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale score, pain intensity on movement score, Visual Analogue Scale (VAS), and overall pain score were obtained.

Results: Out of 10,587 patients, 10,265 completed the present study. The majority of patients had lower back pain (n=3386, 32.99%) and knee pain (n=3184, 31.02%). The average pain intensity on movement score of patients with bursitis significantly decreased from the baseline to 15 days {mean change {95% Confidence Interval (CI)}: 6.04 (5.89, 6.20); p<0.001}. Post-naproxen treatment, the average pain intensity, WOMAC pain score, VAS, and overall pain score significantly decreased from baseline to day 15 in patients with knee pain and lower back pain. A significant improvement in WOMAC, WOMAC pain (5.42 vs 17.98), WOMAC stiffness (1.49 vs 5.75), and WOMAC physical function score (18.93 vs 56.21) at day 15 was observed in patients with a muscle sprain. Adverse Events (AE) were reported in 173 (1.69%) patients overall, with dryness (n=125) being the most common, followed by erythema (n=20) and pruritus (n=17).

Conclusion: Naproxen 10% gel is an effective topical treatment for lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis. It could prove helpful in patients where the side-effects of oral NSAIDs are to be avoided.

Keywords: Anti-inflammatory agent, Topical, Visual analogue scale

INTRODUCTION

Topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been developed as an alternative to oral NSAIDs. Topical NSAIDs were effective in relieving pain in acute conditions such as sprains, strains, and soft tissue injuries, comparable to oral NSAID formulations [1], with minimal risk of AEs related to systemic exposure [2]. They are better suited for use on smaller joints with localised pain as they penetrate the skin to provide effective analgesic concentrations at the site of pain and inflammation [2]. The Osteoarthritis Research Society International guidelines and the National Institute for Health and Care Excellence (NICE) consider topical NSAIDs as safer and better alternatives to oral NSAIDs in the management of Osteoarthritis (OA) [3,4].

Naproxen, an acid derivative of propionic acid, belongs to the NSAIDs class. Naproxen is FDA-approved for treating pain, pyrexia, inflammation, and stiffness produced by OA, rheumatoid arthritis, injuries, tendinitis, bursitis, psoriatic arthritis, gout, ankylosing spondylitis, and tendinitis [5]. Furthermore, they offer the potential to achieve antipyretic and analgesic efficacy and are effective in the treatment of dysmenorrhoea, rheumatoid arthritis, and post-operative pain [6-8]. The half-life for naproxen is 10-18 hours, which is much longer than for several other NSAIDs [9]. Naproxen sodium (440/660 mg) provided significantly greater improvements in pain at rest, on passive motion, on weight-bearing, stiffness after rest (morning), and day and night pain compared to placebo. Naproxen sodium is an alternative in the initial treatment of OA and may be preferred to acetaminophen as first-line therapy in patients with moderate or severe pain [10]. Although several topical NSAIDs were associated with a lower risk of cardiovascular events than oral NSAIDs [11], naproxen has a lesser potential for adverse cardiovascular events than diclofenac and ibuprofen [12].

Although topical NSAIDs are licensed in the Asia-Pacific for osteoarthritic pain, there are no clinical practice guidelines or recommendations for their use in the region [13]. Previous studies have shown some efficacy in topical indomethacin, piroxicam, ketoprofen, and diclofenac for OA and musculoskeletal-related pain [14]. The present study adopts an innovative adjuvant therapy approach, potentially offering complementary treatment options for various conditions such as lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis. Moreover, the study's geographical focus on the Asia-Pacific region is novel, aiming to address the lack of clinical practice guidelines and expand knowledge and awareness of topical NSAID usage in this area. Since the topical formulations reduced pain levels without

any side effects, further studies on this topic have been suggested. To increase awareness and advance the role of topical NSAIDs as a therapeutic option, the present study aimed to evaluate the efficacy and safety of a topically applied NSAID, naproxen 10% gel (naprosyn plus gel), as an adjuvant therapy for lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis.

MATERIALS AND METHODS

A prospective, cohort, observational, open-label, single-arm, multicentric study conducted at 458 centres in India, including Ahmedabad, Bengaluru, Chandigarh, Chennai, Delhi, Guwahati, Hyderabad, Indore, Jaipur, Kolkata, Lucknow, Meerut, Mumbai, Patna, and Pune, between February 2023 and May 2023. A list of all sites is provided in [Annexure-1]. The data was collected from outpatient settings/clinics of orthopaedicians and clinicians who have been prescribing topical naproxen 10% gel to their patients. The study protocol was approved by the Institutional Ethics Committee (Approval no. RPIEC0190223). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and all applicable local Good Clinical Practice (GCP) and regulations. Written informed consent was obtained from each participant.

Inclusion and Exclusion criteria: Patients aged between 18 and 60 years of either sex who were suffering from back pain, muscle pain, sprains, frozen shoulder, arthritis, acute low back ache (non-specific), or pain and inflammation following trauma to muscles due to strains, sprains, stress, and soft tissue injuries with a baseline pain intensity score of >40 were included in the study [15].

Exclusion criteria: Patients who had surgical interventions for low back pain <4 weeks or who had received corticosteroids or opioids <90 days before enrollment, or who required hospitalisation or other treatment for pain. Patients with a history of psoriatic arthritis, spondyloarthropathy, metastatic cancer, Paget's disease, sciatica or spinal stenosis, fibromyalgia, mental illness, or tumours, infected spinal cord, or herniated disc-associated pain. Additionally, patients with skin wounds, open injuries, painful conditions other than sports-related injury/contusion, and patients who were already on oral NSAIDs analgesics, and those who were hypersensitive to naproxen 10% gel were excluded from the study.

Study Procedure

The data was captured during the scheduled follow-up visits planned by the treating clinician. The participating investigator had to record the data at 3, 5, 10, and 15 days. At the baseline visit, demographic details (age, sex, weight, height, body mass index, and symptoms), WOMAC pain subscale score [16], pain intensity on movement score, VAS [17], and overall pain score were obtained. In addition, the WOMAC pain subscale score, pain intensity on movement, VAS, and overall pain score were evaluated after 3, 5, 10, and 15 days of treatment. The WOMAC score ranges from 0 to 96 points, and the questionnaire is divided into three main sections: pain (0-20 points), stiffness (0-8 points), and physical function (0-68 points). Higher index values are associated with more severe symptoms and impaired function [18]. The intensity of pain was evaluated using the 10-point VAS [19].

According to the intensity of the pain, the patients were divided into four groups: mild (<40 mm), moderate (40-60 mm), severe (60-80 mm), and very severe (>80 mm) pain [17]. The WOMAC, pain intensity on movement score, VAS, and overall pain score were assessed for clinical disease severity (pain status and function) on movement. The WOMAC is a self-reported questionnaire completed by the patient, providing information about disease activity and evaluating underlying disease symptoms.

The primary outcome variables were changes from baseline in the total WOMAC pain subscale score, pain intensity on movement score, VAS, and overall pain score after 3, 5, 10, and 15 days of treatment. The secondary outcome was the assessment of adverse events.

STATISTICAL ANALYSIS

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Descriptive statistics were used to describe categorical variables (frequency and percentages) and continuous variables (mean and standard deviation [SD] or median [range] depending on the normality of data). A comparison of qualitative variables between groups was made using the Kruskal-Wallis test for nonparametric variables. A comparison of quantitative variables between groups was made using the Chi-square test. A paired sample t-test was used to compare the pre- and post-treatment variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 10,587 patients were enrolled, of which 10,265 completed the study visits. The demographic characteristics are summarised in [Table/Fig-1]. The majority of patients had lower back pain (32.99%) and knee pain (31.02%). The median time (range) to the onset of action was 10 minutes (6 to 14 minutes) after treatment with naproxen 10% gel.

Parameters	n (%)
Age (years)	48 (22-60)
Gender	
Men	5545 (54.02)
Women	4720 (45.98)
Weight (kg)	69 (40-90)
Height (m)	1.68 (1.47-18.60)
BMI (kg/m^2)	24.51 (16.65-34.13)
Symptoms	
Lower back pain	3386 (32.99)
Knee pain	3184 (31.02)
Cervical pain	2770 (26.98)
Synovitis	308 (3)
Bursitis	207 (2)
Muscle sprain	205 (2)
Tendinitis	205 (2)
Pain intensity on movement	9 (5-10)
WOMAC index score	
Pain	17 (13-20)
Stiffness	7 (3-8)
Physical function	59 (54-67)
VAS	9 (6-10)
Onset of action (min)	10 (6-14)
Overall pain	9 (6-10)

[Table/Fig-1]: Demographic characteristics (N=10265).
Data shown as, median (range), unless otherwise specified
BMI: Body mass index; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster universities osteoarthritis index

Change in different score parameters:

Bursitis: The average pain intensity on movement score significantly decreased from baseline to 15 days (mean change [95% CI]: 6.04 [5.89, 6.20]; p<0.001). After the five day follow-up, the WOMAC pain score of bursitis improved significantly from baseline (17.31 vs 9.79) until the last follow-up visit (17.31 vs 4.72). Naproxen 10% gel demonstrated statistically significant improvement in WOMAC stiffness and WOMAC physical function on day 15. Over the subsequent follow-up visits, the average VAS decreased to 2.73 with a mean change of 5.77. The overall pain score significantly

decreased from baseline to day 15 (mean change [95% CI]: 5.71 [5.50, 5.93]; p<0.001) [Table/Fig-2].

Cervical pain: The average pain intensity on movement score significantly decreased from baseline to day 15 (mean change [95% CI]: 6.66 [6.61, 6.72]; p<0.001). Naproxen 10% gel demonstrated statistically significant improvement in WOMAC pain, stiffness, and physical function on day 15. Over the subsequent follow-up visits, the average VAS and overall pain score decreased to 2.11 and 1.84 with mean changes of 6.44 and 6.86, respectively [Table/Fig-2].

Knee pain: The average pain intensity on movement score significantly decreased from baseline to day 15 (8.92 vs 2.43). There was a significant improvement in WOMAC pain, stiffness, and physical function score on day 15. Over the subsequent follow-up visits, the average VAS and overall pain score decreased to 2.31 and 2.07 with mean changes of 6.29 and 6.73, respectively [Table/Fig-2].

Lower back pain: The average pain intensity on movement score significantly decreased from baseline to day 15 (mean change [95% CI]: 6.41 [6.36, 6.46]; p<0.001). After the five-day follow-up, the WOMAC pain score of lower back pain improved significantly from baseline (10.19 vs 16.91) until the last follow-up visit (4.79 vs 16.91). Naproxen 10% gel demonstrated statistically significant improvement in WOMAC stiffness and physical function on day 15. Over the subsequent follow-up visits, the mean pain VAS and overall pain scores reduced from 8.44 to 2.14 (p<0.001) and 8.63 to 2.04 (p<0.001), respectively.

Muscle sprain: The average pain intensity on movement score significantly decreased from baseline to day 15 (1.70 vs 8.32). There was a significant improvement in WOMAC pain, stiffness, and physical function score at day 15. Over the subsequent follow-up visits, the average VAS and overall pain score decreased to 0.89 and 0.83 with mean changes of 7.35 and 7.39, respectively.

Synovitis: The average pain intensity on movement score significantly decreased from baseline to day 15 (8.16 vs 2.33; p<0.001). There was a significant improvement in WOMAC pain, stiffness, and physical function score at day 15 (p<0.001, each). Over the subsequent follow-up visits, the average VAS and overall pain score decreased to 2.23 and 2.18, with mean changes of 5.91 and 6.01, respectively.

Tendinitis: The average pain intensity on movement score significantly decreased from baseline to day 15 (8.22 vs 1.95; p<0.001). There was a significant improvement in WOMAC pain, stiffness, and physical function score from baseline to day 15. Over the subsequent follow-up visits, the average VAS and overall pain score decreased to 1.89 and 2.00, with mean changes of 6.19 and 6.82, respectively [Table/Fig-2].

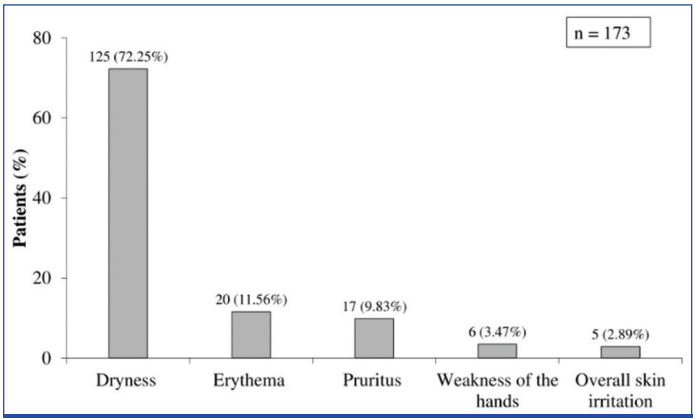
Adverse Events (AE): A total of 173 (1.69%) patients reported adverse events during the study period. The most commonly reported AEs were dryness (72.25%), followed by erythema (11.56%), pruritus (9.83%), weakness of hands (3.47%), and overall skin irritation (2.89%) [Table/Fig-3].

Parameters	Baseline	Day 3	Day 5	Day 10	Day 15
Bursitis (n=207)					
Pain intensity on movement, mean (SD)	9.21 (0.96)	8.04 (1.21)	5.05 (1.77)	4.14 (1.52)	3.17 (0.97)
Mean difference (95% CI); p-value	-	1.17 (1.02, 1.32); p<0.001	4.16 (3.89, 4.44); p<0.001	5.08 (4.86, 5.30); p<0.001	6.04 (5.89, 6.20); p<0.001
WOMAC pain, mean (SD)	17.31 (1.24)	13.64 (1.27)	9.79 (1.15)	7.76 (1.43)	4.72 (1.50)
Mean difference (95% CI); p-value	-	3.68 (3.46, 3.89); p<0.001	7.53 (7.31, 7.75); p<0.001	9.56 (9.32, 9.79); p<0.001	12.59 (12.34, 12.85); p<0.001
WOMAC stiffness, mean (SD)	6.32 (0.76)	4.75 (0.78)	3.73 (0.78)	3.41 (0.70)	1.86 (0.61)
Mean difference (95% CI); p-value	-	1.57 (1.47, 1.67); p<0.001	2.58 (2.47, 2.70); p<0.001	2.91 (2.76, 3.06); p<0.001	4.45 (4.33, 4.58); p<0.001
WOMAC physical function, mean (SD)	58.36 (2.14)	46.95 (1.53)	39.08 (2.79)	34.40 (0.79)	22.56 (2.17)
Mean difference (95% CI); p-value	-	11.42 (10.95, 11.88); p<0.001	19.29 (19.02, 19.55); p<0.001	23.96 (23.60, 24.32); p<0.001	35.81 (35.41, 36.20); p<0.001
VAS, mean (SD)	8.51 (1.39)	8.20 (0.84)	4.85 (1.80)	4.02 (1.58)	2.73 (0.75)
Mean difference (95% CI); p-value	-	0.31 (0.05, 0.57); p<0.001	3.66 (3.54, 3.79); p<0.001	4.49 (4.35, 4.63); p<0.001	5.77 (5.55, 6.00); p<0.001
Overall pain, mean (SD)	8.46 (1.40)	7.86 (1.01)	5.68 (2.71)	4.03 (1.57)	2.75 (0.71)
Mean difference (95% CI); p-value	-	0.60 (0.78, 0.42); p<0.001	2.78 (2.57, 2.99); p<0.001	4.43 (4.29, 4.57); p<0.001	5.71 (5.50, 5.93); p<0.001
Cervical pain (n=2770)					
Pain intensity on movement, mean (SD)	8.78 (1.00)	6.86 (1.31)	4.89 (0.94)	3.02 (1.13)	2.11 (1.05)
Mean difference (95% CI); p-value	-	1.92 (1.87, 1.96); p<0.001	3.88 (3.83, 3.94); p<0.001	5.76 (5.70, 5.81); p<0.001	6.66 (6.61, 6.72); p<0.001
WOMAC pain, mean (SD)	17.20 (1.57)	13.83 (1.72)	10.45 (1.52)	8.48 (1.90)	5.10 (1.73)
Mean difference (95% CI); p-value	-	3.36 (3.31, 3.42); p<0.001	6.74 (6.66, 6.83); p<0.001	8.72 (8.63, 8.80); p<0.001	12.10 (12.02, 12.18); p<0.001
WOMAC stiffness, mean (SD)	6.59 (1.25)	5.34 (1.41)	4.09 (1.07)	3.11 (1.14)	1.58 (0.94)
Mean difference (95% CI); p-value	-	1.25 (1.22, 1.28); p<0.001	2.50 (2.46, 2.54); p<0.001	3.48 (3.42, 3.55); p<0.001	5.01 (4.96, 5.06); p<0.001
WOMAC physical function, mean (SD)	59.21 (2.34)	47.01 (2.55)	40.00 (2.67)	34.22 (2.24)	20.79 (3.84)
Mean difference (95% CI); p-value	-	12.20 (12.05, 12.34); p<0.001	19.22 (19.08, 19.35); p<0.001	25.00 (24.87, 25.12); p<0.001	38.43 (38.29, 38.57); p<0.001
VAS, mean (SD)	8.55 (1.12)	6.69 (1.14)	4.74 (0.85)	2.94 (1.06)	2.11 (1.06)
Mean difference (95% CI); p-value	-	1.86 (1.81, 1.91); p<0.001	3.81 (3.76, 3.86); p<0.001	5.61 (5.56, 5.67); p<0.001	6.44 (6.38, 6.51); p<0.001
Overall pain, mean (SD)	8.70 (1.04)	6.95 (1.32)	5.06 (1.16)	3.03 (1.09)	1.84 (0.95)
Mean difference (95% CI); p-value	-	1.75 (1.70, 1.80); p<0.001	3.63 (3.58, 3.68); p<0.001	5.66 (5.61, 5.71); p<0.001	6.86 (6.81, 6.91); p<0.001

Knee pain (n=3184)					
Pain intensity on movement, mean (SD)	8.92 (0.94)	6.97 (1.46)	4.71 (1.19)	3.25 (1.24)	2.43 (1.18)
Mean difference (95% CI); p-value	-	1.95 (1.90, 2.00); p<0.001	4.22 (4.16, 4.27); p<0.001	5.68 (5.63, 5.72); p<0.001	6.50 (6.44, 6.55); p<0.001
WOMAC pain, mean (SD)	17.00 (1.47)	13.97 (1.59)	10.60 (1.64)	8.75 (1.47)	5.03 (1.58)
Mean difference (95% CI); p-value	-	3.03 (2.98, 3.07); p<0.001	6.39 (6.32, 6.47); p<0.001	8.25 (8.18, 8.32); p<0.001	11.97 (11.89, 12.05); p<0.001
WOMAC stiffness, mean (SD)	6.38 (1.18)	5.04 (1.19)	3.92 (0.99)	2.90 (1.05)	1.41 (0.93)
Mean difference (95% CI); p-value	-	1.34 (0.77, 0.01); p<0.001	2.46 (1.18, 0.02); p<0.001	3.48 (1.51, 0.03); p<0.001	4.98 (1.50, 0.03); p<0.001
WOMAC physical function, mean (SD)	59.37 (2.62)	46.56 (2.76)	40.48 (3.07)	34.17 (1.83)	20.83 (4.01)
Mean difference (95% CI); p-value	-	12.80 (12.67, 12.94); p<0.001	18.88 (18.75, 19.01); p<0.001	25.19 (25.09, 25.30); p<0.001	38.54 (38.40, 38.68); p<0.001
VAS, mean (SD)	8.60 (1.10)	6.79 (1.29)	4.67 (1.17)	3.08 (1.14)	2.31 (1.12)
Mean difference (95% CI); p-value	-	1.81 (1.76, 1.86); p<0.001	3.93 (3.88, 3.99); p<0.001	5.52 (5.48, 5.56); p<0.001	6.29 (6.22, 6.35); p<0.001
Overall pain, mean (SD)	8.79 (1.09)	7.12 (1.46)	5.02 (1.56)	3.09 (1.14)	2.07 (1.15)
Mean difference (95% CI); p-value	-	1.67 (1.62, 1.72); p<0.001	3.77 (3.71, 3.83); p<0.001	5.70 (5.66, 5.74); p<0.001	6.73 (6.66, 6.79); p<0.001
Lower back pain (n=3386)					
Pain intensity on movement, mean (SD)	8.58 (1.03)	7.16 (1.46)	4.92 (0.93)	3.13 (0.90)	2.16 (0.95)
Mean difference (95% CI); p-value	-	1.42 (1.36, 1.47); p<0.001	3.66 (3.61, 3.71); p<0.001	5.45 (5.40, 5.50); p<0.001	6.41 (6.36, 6.46); p<0.001
WOMAC pain, mean (SD)	16.91 (1.55)	13.73 (1.75)	10.19 (1.61)	8.41 (1.61)	4.79 (1.52)
Mean difference (95% CI); p-value	-	3.18 (3.14, 3.22); p<0.001	6.72 (6.65, 6.79); p<0.001	8.51 (8.43, 8.58); p<0.001	12.12 (12.06, 12.18); p<0.001
WOMAC stiffness, mean (SD)	6.49 (1.30)	5.16 (1.20)	4.07 (1.07)	3.04 (0.93)	1.51 (0.90)
Mean difference (95% CI); p-value	-	1.34 (1.30, 1.37); p<0.001	2.42 (2.38, 2.47); p<0.001	3.45 (3.40, 3.50); p<0.001	4.98 (4.93, 5.03); p<0.001
WOMAC physical function, mean (SD)	59.41 (2.64)	46.83 (2.66)	40.28 (2.73)	33.84 (2.16)	20.35 (3.63)
Mean difference (95% CI); p-value	-	12.58 (12.46, 12.70); p<0.001	19.13 (19.02, 19.25); p<0.001	25.57 (25.47, 25.67); p<0.001	39.06 (38.92, 39.20); p<0.001
VAS, mean (SD)	8.44 (1.06)	7.09 (1.41)	4.80 (0.88)	3.05 (0.86)	2.14 (0.94)
Mean difference (95% CI); p-value	-	1.35 (1.30, 1.40); p<0.001	3.64 (3.59, 3.69); p<0.001	5.39 (5.34, 5.43); p<0.001	6.30 (6.25, 6.35); p<0.001
Overall pain, mean (SD)	8.63 (0.98)	7.37 (1.41)	5.09 (1.16)	3.15 (0.92)	2.04 (0.90)
Mean difference (95% CI); p-value	-	1.26 (1.21, 1.31); p<0.001	3.54 (3.49, 3.59); p<0.001	5.48 (5.44, 5.53); p<0.001	6.59 (6.54, 6.63); p<0.001
Muscle sprain (n=205)					
Pain intensity on movement, mean (SD)	8.32 (0.79)	5.97 (1.17)	5.23 (0.91)	3.69 (1.91)	1.70 (0.80)
Mean difference (95% CI); p-value	-	2.36 (2.21, 2.50); p<0.001	3.09 (2.90, 3.28); p<0.001	4.63 (4.32, 4.93); p<0.001	6.62 (6.48, 6.76); p<0.001
WOMAC pain, mean (SD)	17.98 (1.09)	14.19 (1.21)	10.39 (1.53)	9.31 (1.63)	5.42 (1.03)
Mean difference (95% CI); p-value	-	3.79 (3.70, 3.88); p<0.001	7.59 (7.26, 7.92); p<0.001	8.67 (8.34, 9.00); p<0.001	12.56 (12.34, 12.78); p<0.001
WOMAC stiffness, mean (SD)	5.75 (1.47)	4.98 (1.08)	4.35 (0.79)	2.30 (0.67)	1.49 (1.34)
Mean difference (95% CI); p-value	-	0.77 (0.67, 0.86); p<0.001	1.40 (1.24, 1.56); p<0.001	3.44 (3.24, 3.65); p<0.001	4.25 (4.13, 4.37); p<0.001
WOMAC physical function, mean (SD)	56.21 (2.77)	47.27 (3.15)	38.56 (1.72)	32.46 (1.40)	18.93 (2.87)
Mean difference (95% CI); p-value	-	8.95 (8.22, 9.68); p<0.001	17.65 (17.30, 18.01); p<0.001	23.75 (23.45, 24.06); p<0.001	37.29 (36.95, 37.62); p<0.001
VAS, mean (SD)	8.24 (0.76)	5.73 (0.81)	5.32 (0.77)	3.38 (1.42)	0.89 (0.92)
Mean difference (95% CI); p-value (95% CI); p-value	-	2.51 (2.38, 2.64); p<0.001	2.92 (2.75, 3.08); p<0.001	4.86 (4.64, 5.08); p<0.001	7.35 (7.20, 7.49); p<0.001
Overall pain, mean (SD)	8.22 (0.67)	5.90 (1.04)	5.17 (0.86)	3.39 (1.38)	0.83 (0.87)
Mean difference (95% CI); p-value	-	2.33 (2.19, 2.47); p<0.001	3.06 (2.88, 3.23); p<0.001	4.83 (4.62, 5.05); p<0.001	7.39 (7.27, 7.51); p<0.001
Synovitis (n=308)					
Pain intensity on movement, mean (SD)	8.16 (0.87)	7.33 (1.63)	4.78 (1.24)	3.09 (0.94)	2.33 (0.69)
Mean difference (95% CI); p-value	-	0.82 (0.67, 0.98); p<0.001	3.38 (3.18, 3.58); p<0.001	5.06 (4.89, 5.24); p<0.001	5.82 (5.72, 5.92); p<0.001
WOMAC pain, mean (SD)	17.72 (0.92)	15.01 (1.30)	10.79 (1.09)	9.38 (0.95)	4.81 (1.17)
Mean difference (95% CI); p-value	-	2.71 (2.59, 2.84); p<0.001	6.94 (6.78, 7.10); p<0.001	8.35 (8.20, 8.50); p<0.001	12.92 (12.73, 13.10); p<0.001

WOMAC stiffness, mean (SD)	6.71 (1.06)	4.63 (0.90)	3.86 (0.77)	3.01 (0.55)	1.60 (0.65)
Mean difference (95% CI); p-value	-	2.07 (1.94, 2.21); p<0.001	2.85 (2.69, 3.00); p<0.001	3.69 (3.55, 3.84); p<0.001	5.11 (4.99, 5.23); p<0.001
WOMAC physical function, mean (SD)	57.28 (2.27)	46.37 (2.49)	41.52 (3.75)	34.45 (2.13)	17.75 (2.52)
Mean difference (95% CI); p-value	-	10.90 (10.47, 11.34); p<0.001	15.75 (15.31, 16.19); p<0.001	22.82 (22.56, 23.09); p<0.001	39.53 (39.15, 39.91); p<0.001
VAS, mean (SD)	8.14 (0.88)	7.23 (1.57)	4.68 (1.22)	3.04 (0.87)	2.23 (0.60)
Mean difference (95% CI); p-value	-	0.91 (0.76, 1.06); p<0.001	3.46 (3.26, 3.67); p<0.001	5.10 (4.92, 5.27); p<0.001	5.91 (5.81, 6.01); p<0.001
Overall pain, mean (SD)	8.19 (0.91)	7.22 (1.66)	4.82 (1.28	3.02 (0.89)	2.18 (0.75)
Mean difference (95% CI); p-value	-	0.96 (0.81, 1.12); p<0.001	3.37 (3.18, 3.56); p<0.001	5.17 (4.99, 5.35); p<0.001	6.01 (5.90, 6.12); p<0.001
Tendinitis (n=205)					
Pain intensity on movement, mean (SD)	8.22 (1.01)	7.16 (1.18)	5.04 (1.85)	2.38 (0.97)	1.95 (1.08)
Mean difference (95% CI); p-value	-	1.07 (0.81, 1.33); p<0.001	3.19 (2.81, 3.56); p<0.001	5.85 (5.69, 6.01); p<0.001	6.27 (6.00, 6.55); p<0.001
WOMAC pain, mean (SD)	15.42 (1.38)	12.45 (2.10)	8.92 (1.05)	6.66 (2.26)	3.50 (1.44)
Mean difference (95% CI); p-value	-	2.97 (2.83, 3.11); p<0.001	6.50 (6.35, 6.64); p<0.001	8.76 (8.56, 8.96); p<0.001	11.92 (11.80, 12.04); p<0.001
WOMAC stiffness, mean (SD)	6.85 (1.00)	5.73 (1.10)	3.96 (1.00)	3.30 (0.80)	1.87 (1.04)
Mean difference (95% CI); p-value	-	1.12 (1.06, 1.18); p<0.001	2.89 (2.82, 2.96); p<0.001	3.55 (3.44, 3.66); p<0.001	4.98 (4.89, 5.06); p<0.001
WOMAC physical function, mean (SD)	59.08 (1.77)	43.90 (2.44)	38.72 (1.09)	34.10 (0.80)	23.36 (3.53)
Mean difference (95% CI); p-value	-	15.18 (14.62, 15.73); p<0.001	20.36 (20.00, 20.71); p<0.001	24.98 (24.71, 25.26); p<0.001	35.72 (35.29, 36.15); p<0.001
VAS, mean (SD)	8.08 (1.00)	6.99 (1.12)	3.92 (0.99)	2.23 (0.60)	1.89 (1.01)
Mean difference (95% CI); p-value	-	1.10 (0.84, 1.35); p<0.001	4.16 (3.95, 4.37); p<0.001	5.85 (5.70, 6.00); p<0.001	6.19 (5.93, 6.45); p<0.001
Overall pain, mean (SD)	8.82 (0.70)	7.10 (1. 01)	3.88 (0.87)	2.32 (0.67)	2.00 (1.06)
Mean difference (95% CI); p-value	-	1.72 (1.56, 1.88); p<0.001	4.94 (4.78, 5.10); p<0.001	6.50 (6.38, 6.63); p<0.001	6.82 (6.65, 7.00); p<0.001

[Table/Fig-2]: Change in different score parameters.
VAS: Visual analogue scale; WOMAC: Western ontario and mcmaster universities osteoarthritis index
A paired sample t-test was used and p<0.05 was considered statistically significant



[Table/Fig-3]: Adverse Events (AE).
Data shown as n (%)

Comparative analysis: The occurrence of AEs was more likely among patients with bursitis (33.33%) compared to patients with muscle sprain (7.80%), synovitis (3.25%), tendinitis (1.95%), cervical pain (1.52%), lower back pain (0.74%), and knee pain (0.22%) [Table/Fig-4].

DISCUSSION

Naproxen 10% gel has shown to be a clinically significant therapeutic agent for reducing pain and improving function in patients with arthritis [20]. However, there is a scarcity of data from India evaluating the clinical efficacy and safety of topical NSAIDs, highlighting the need for such studies. The present study aimed to evaluate the efficacy and safety of naproxen 10% gel in patients with lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis. The main findings of the study were:

Parameters	Bursitis (n=207) n (%)	Cervical pain (n=2770) n (%)	Knee pain (n=3184) n (%)	Lower back pain (n=3386) n (%)	Muscle sprain (n=205) n (%)	Synovitis (n=308) n (%)	Tendinitis (n=205) n (%)	p-value
Gender								
Men	131 (63.29)	1490 (53.79)	1671 (52.48)	1897 (56.02)	27 (13.17)	151 (49.03)	178 (86.83)	<0.001
Women	76 (36.71)	1280 (46.21)	1513 (47.52)	1489 (43.98)	178 (86.83)	157 (50.97)	27 (13.17)	
Adverse Events (AE)	69 (33.33)	42 (1.52)	7 (0.22)	25 (0.74)	16 (7.80)	10 (3.25)	4 (1.95)	<0.001
Dryness	51 (73.91)	35 (83.33)	-	21 (84.0)	11 (68.75)	5 (50.0)	2 (50.0)	
Erythema	8 (11.59)	3 (7.14)	4 (57.14)	-	4 (25.0)	-	1 (25.0)	
Overall skin irritation	1 (1.45)	-	-	4 (16.0)	-	-	-	<0.001
Pruritus	7 (10.14)	4 (9.52)	3 (42.86)	-	-	3 (30.0)	-	
Weakness of the hands	2 (2.90)	-	-	-	1 (6.25)	2 (20.0)	1 (25.0)	

[Table/Fig-4]: Comparative analysis.
BMI: Body mass index; PF: Physical function; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster universities osteoarthritis index

i) The majority of patients had lower back pain and knee pain; ii) The median time to onset of action was 10.00 min; iii) Naproxen 10% gel significantly improved pain intensity on movement, WOMAC, VAS, and overall pain scores ($p<0.05$); iv) AEs were more likely to occur among patients with bursitis.

Bursitis: The average pain intensity on movement score significantly decreased from baseline to day 15 (mean change: 6.04). Similarly, during subsequent follow-up, the WOMAC subscale and VAS scores of bursitis improved significantly from baseline during treatment with topical naproxen 10% gel. Homayouni K et al., demonstrated that treatment of anserinus tendinobursitis with oral naproxen was effective in reducing pain VAS score ($Z=-3.45$, $p=0.001$) and swelling score ($Z=-4.14$, $p=0.0001$) [21].

Cervical pain: Wong JJ et al., found that NSAIDs may be more effective than placebo in patients with neck pain and associated disorders [22]. However, there are a small number of well-performed trials for neck pain, and the authors were unable to locate randomised controlled trials examining naproxen use specifically for neck pain. Oral indomethacin and piroxicam were more effective in reducing pain in patients with cervical pain [23]. Another trial compared intramuscular ketorolac to the manipulation of cervical pain and found statistically significant between-group differences in pain reduction favouring NSAIDs [24]. Furthermore, oral naproxen formulation alone produced the most significant effect during the various stages of pain perception assessment [25]. However, in the present study, the efficacy of naproxen 10% gel was evaluated in patients with cervical pain. The astounding finding in the present study was a significant improvement in pain intensity on movement, WOMAC score, VAS, and overall pain scores from baseline to day 15. A multicentre randomised controlled study assessed the efficacy and safety of topically applied diclofenac plus capsaicin gel over a four-day treatment period. The change from baseline in pain on movement score at day two was superior in the combination group compared to diclofenac alone (mean difference: -3.05 cm vs -2.33 cm). However, the incidence of erythema was higher in the diclofenac plus capsaicin gel-treated groups [26]. More than half of diclofenac diethylamine 1.16% gel patients (58.3%) showed an early response to treatment with a mean reduction in pain on movement VAS score. However, in the present study, naproxen 10% gel reported better early improvement in all patients with cervical pain [27].

Knee pain: Svensson O et al., evaluated the relative improvement in hip and knee OA during treatment with a twice-daily oral dose of naproxen. There was a significant improvement in knee pain for WOMAC pain (mean change=4.7 mm; $p=0.03$), WOMAC stiffness (mean change=6.6 mm; $p=0.004$), and WOMAC physical function (mean change=4.8 mm; $p=0.016$) at week 6 [28]. Another randomised controlled study evaluated the analgesic efficacy and safety of naproxen sodium for short-term use in patients with OA. The mean changes in pain at rest (0.6 vs 0.4), pain on passive motion (0.7 vs 0.4), and pain on weight bearing (1.1 vs 0.8) were significantly greater in the naproxen sodium group compared to the placebo group [29]. Results from a recently conducted network meta-analysis by Jevsevar DS et al., revealed that naproxen had the highest probability of improving function and clinical significance compared to placebo [30]. Similarly, the present study reported a more significant improvement in knee patients during treatment with topical naproxen 10% gel. The mean changes from baseline in the VAS and overall pain parameters were also significantly decreased ($p<0.05$) with naproxen 10% gel. An in-vivo study by Noreen S et al., also showed that the optimised gel formulation was more effective in treating arthritis-associated inflammation [31]. In contrast, Essex MN et al., noted that although there was an improvement in WOMAC stiffness from baseline in the naproxen-treated group (-1.9 vs -1.6), the differences between oral naproxen and placebo were not statistically significant [32]. Wadsworth LT et al., reported that after treatment with diclofenac 1.5% solution, the mean change in WOMAC pain, WOMAC stiffness, and WOMAC physical function score from baseline was 4.5, 1.7, and 14.3, respectively [33], which was lower than the mean difference observed in the present study with naproxen 10% gel (11.97, 4.98, and 38.54, respectively). Interestingly, the baseline pain scores in the patient population were also higher than those reported in Wadsworth LT et al., [33]. Results from a recent network meta-analysis of randomised controlled trials and observational studies revealed a significant improvement in pain relief score for diclofenac solution [mean difference: -0.29], diclofenac gel (mean difference: 0.30), and diclofenac patches (mean difference: -0.94), however, these differences were lower than the results reported in the present study [14].

Lower back pain: Naproxen 10% gel demonstrated a statistically significant improvement in average pain intensity on movement, WOMAC, VAS, and overall pain scores from baseline in patients with lower back pain. A twice-daily oral dose of naproxen was also effective in reducing low back pain in a total of 93.1% of patients. Regarding pain severity, the average value of VAS was reduced by 6.2 times compared to baseline [34]. On another note, a previous study by Bhattarai S et al., compared the efficacy of aceclofenac, naproxen, diclofenac, and nimesulide in patients with acute lumbago and resulted in a more effective profile of aceclofenac than other forms of NSAIDs [35].

Muscle sprain: Butrón F et al., evaluated the efficacy and safety of naproxen and diclofenac gel in patients with contusions and sprains. The results showed that both drugs resulted in a significant reduction in pain modalities, oedema, and functional alterations ($p<0.001$). However, naproxen gel reduced spontaneous pain slightly better than diclofenac gel [36]. Similarly, the present study showed a favourable mean reduction in muscle sprain WOMAC pain (17.98 vs 5.42), WOMAC stiffness (5.75 vs 1.49), and WOMAC physical function score (56.21 vs 18.93) from baseline to day 15 in patients with naproxen 10% gel. This indicates optimal improvement in pain associated with a muscle sprain. Several previous clinical studies have reported better efficacy of topical NSAIDs in the treatment of muscle sprain. A previously published multicentre, double-blind, randomised controlled study observed a significant reduction in pain after two weeks of treatment with this diclofenac patch in patients with sports injuries [37]. Similarly, Ibuprofen cream has also been shown to significantly reduce pain associated with acute soft tissue injury during a 48-hour treatment period [38].

Synovitis: Inflammation of the synovial tissue is an emerging feature of OA, even in the early stages of the disease [39]. The addition of naproxen results in the inhibition of NF-κB activation and reduces the production of IL-6 by human OA synovial tissue [40,41]. Similarly, the present study showed a clinically valuable reduction in WOMAC and VAS pain scores in patients with synovitis. These observations demonstrate the safe and effective use of naproxen 10% gel in patients with synovitis. Cui XD and Liu XF demonstrated a significant improvement in pain, swelling, and restricted movement in patients with knee synovitis from baseline after two-week regimen of Cortex Daphnes patch compared with the control group (45.73 vs 55.73) [42]. The decline of knee joint function score was significantly better in the plaster group than in the control group [42].

Tendinitis: According to the results reported by Thorling J et al., which depicted the clinical efficacy of naproxen gel in patients with tendinitis, the present study also showed that patients treated with naproxen 10% gel improved more rapidly and had significantly lower severity scores for all symptoms ($p<0.05$) during the course of the study [43]. Seligra A et al., concluded that naproxen gel was associated with a marked and rapid reduction in pain on passive movement, tenderness to firm palpation, swelling, and a

tendency towards lower rates of gel usage compared to patients using flufenamic acid [44]. Similarly, Baixauli F et al., noted marked relief from pain associated with deep palpation in patients using naproxen gel [45]. Chhetri RS et al., evaluated the efficacy of diclofenac Phonophoresis (PP) with methylprednisolone injection in patients with acute calcific tendinitis of the shoulder. The diclofenac PP with methylprednisolone injection provided substantial short-term improvement of shoulder function in tendinitis within a week; however, long-term improvement was non-significant [46].

The most common Adverse Events (AEs) observed were dryness (72.25%), followed by erythema (11.56%), pruritus (9.83%), weakness of hands (3.47%), and overall skin irritation (2.89%). AEs were more likely to be observed among patients with bursitis. The low magnitude of risk for AEs with naproxen 10% gel in the present study was consistent with what has been demonstrated in a previous report [20].

Limitation(s)

The authors acknowledge a few limitations of the present study. First, the 15-day treatment period is short to assess the ability to maintain the efficacy of topical naproxen 10% gel in treating symptomatic arthritis and musculoskeletal-related pain. The study, therefore, paves the way for longer-duration studies with the objective of analysing long-term efficacy and safety for more precise estimates of results.

CONCLUSION(S)

The present study has demonstrated that topical application of naproxen 10% gel reduced pain associated with lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis, which showed more rapid and significantly superior improvement compared to baseline scores. It is concluded that naproxen 10% gel is an effective topical treatment for lower back pain, knee pain, cervical pain, synovitis, bursitis, muscle sprain, and tendinitis, which could prove helpful in patients where the side effects of oral NSAIDs are to be avoided.

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