VOLUME-6 | ISSUE-1 | JANUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

A Study comparing effect of Generic Diclofenac Sodium Topical gel, 1% to Volteran Gel (Diclofenac sodium topical gel) 1 % in the treatment of subjects with Osteoarthritis of the knee.

Orthopaedic

KEYWORDS: Osteoarthritis, Diclofenac sodium gel,

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ABSTRACT

Background: Osteoarthritis (OA) is a highly prevalent chronic joint disease characterized by cartilage loss, synovial inflammation and bone remodeling. Occurring most frequently in the knee, the prevalence of OA in this joint increases with age. International guidelines for osteoarthritis care recommend considering use of topical NSAIDs as an alternative to oral NSAIDS. **Objectives:** The current study was designed to determine the therapeutic equivalence and safety of a topical application of generic Diclofenac sodium gel, 1% (Test Product) compared to Voltaren (Diclofenac sodium topical gel), 1% (Reference Product) in subjects with osteoarthritis of the knee. **Material and Methods:** Patients undergoing treatment for primary osteoarthritis of the knee, on O.P.D. basis were included in this study. The study followed a double - blind, randomized, vehicle controlled, parallel group design. Subjects meeting all entry criteria were randomly assigned to one of the three treatment groups in a 1:1:1 ratio. **Results:** There was a significant improvement in WOMAC pain score over 3 visits (0,2,4 weeks). 1% diclofenac gel showed comparable results against Volteran gel. Drug was relatively safe with no reported AEs or SAEs in either arm. Conclusion: Diclofenac sodium topical gel combines low systemic toxicity exposure to diclofenac with effective analgesia and potential tolerability benefits for adult patients with OA pain regardless of age.

Introduction:

Osteoarthritis (OA) is a highly prevalent chronic degenerative joint disease which is characterized by cartilage loss, synovia inflammation and bone remodeling.[1] Occurring most frequently in the knee, the prevalence of OA in this joint increases with age, from approximately 1% in people aged 34 years to 30% in people aged 75 years.[2,3] The clinical manifestations of OA include joint pain, stiffness,restricted motion and crepitus (creaking or crackling) on motion. OA is associated with substantial disability and diminished productivity.[4]

Current pharmacotherapy for pain associated with knee OA that does not respond to paracetamol (acetaminophen) includes the oral use of non-steroidal anti-inflammatory drugs (NSAIDs), either nonselective or cyclooxygenase-2 (COX-2) selective.[5] Though effective, NSAIDs have been associated with risks of gastrointestinal, cardiovascular and renal adverse events. Although the incidence of gastrointestinal complications has been reported to be lower with COX-2-selective than with nonselective NSAIDs, the former have been linked to adverse renal effects and an increased risk of cardiovascular complications.[6,7]

International OA guidelines recommend administering NSAIDs at the lowest effective dose for the shortest period of time to minimize the risk of dose-related AEs.[8] As an alternative to oral NSAIDs in patients with heightened risk of AEs, the Osteoarthritis Research Society International (CARSI) and European League Against Rheumatism guidelines recommend topical NSAIDs as a therapeutic option, with an efficacy similar to oral NSAIDs and an AE profile similar to placebo. American Geriatrics Society guidelines published in 2009 also recommend topical NSAIDs for pain in the elderly.[9]

NSAIDs applied topically could achieve therapeutic concentrations in the tissues proximal to the application site with only low, relatively safe serum concentrations.[10] This would avoid adverse GI events, eliminate first pass metabolism, and reduce risk of adverse events related to the high serum drug concentrations often needed for efficacy with systemic dosage forms.[11]

Diclofenac sodium is an NSAID with anti-inflammatory, anti-nociception, and antipyretic effects and has been in widespread therapeutic use for approximately 30 years. Diclofenac sodium inhibits the enzyme, cyclooxygenase (COX), an early component in the arachidonic acid cascade. By inhibiting Cox, diclofenac prevents the formation of thromboxanes, prostaglandins and prostacyclin. Diclofenac also inhibits the production of leukotrienes by decreasing arachidonic acid release and increasing its uptake. Diclofenac is among the most effective inhibitors of prostaglandin E2 (PGE2) production.[5,12]

Aim and Objectives:

The current study was designed to determine the therapeutic equivalence and safety of a topical application of generic Diclofenac sodium gel, 1% (Test Product) compared to Voltaren (Diclofenac sodium topical gel), 1% (Reference Product) in subjects with osteoarthritis of the knee.

Material and Methods:

Patients undergoing treatment for primary osteoarthritis of the knee at M.V. Hospital and Research Centre, Mirza Mandi, Lucknow, on O.P.D. basis were included in this study. The primary outcome measures was done by Western Ontario McMaster Osteoarthritis (WOMAC) pain score which was be measured at baseline and after 4 weeks of gel administration. The study followed a double - blind, randomized, vehicle controlled, parallel group design. Subjects meeting all entry criteria were randomly assigned to one of the three treatment groups in a 1:1:1 ratio (Test: Reference: Vehicle) at baseline visit (Day 0).

Inclusion Criteria:

1. Evidence of a signed and dated informed consent document(s) indicating that the subject has been informed of all pertinent aspects of the study.

2. Healthy, ambulatory male or non pregnant female subjects aged >35 with a clinical diagnosis of OA of the knee including:

a) Presence of at least 3 of the American College of Rheumatology (ACR) criteria (age >50; stiffness lasting <30 mins; bony tenderness; crepitus; bony enlargement ; no palpable warmth)

b) Symptoms of at least 6 months prior to screening, AND

c) Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as buritis, tendonitis , etc.), AND

d) The pain in the target knee required the use of NSAIDS or paracetamol/acetaminophen (topical or oral treatments).

3. Had an Xray of the target knee, taken no more than 1 year before baseline, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease.

4. After discontinuing all pain medications for at least 7 days, has at least moderate pain on movement (POM) for target knee, defined as a baseline score of >50 mm on a 0-100 mm Visual Analogue Scale (VAS) immediately prior to randomisation, AND a baseline WOMAC pain subscale of at least 9 immediately prior to randomization.

5. If female and of child bearing potential, agree to abstain from sexual intercourse or use of a reliable method of contraception during the study.

6. Able to tolerate rescue medication with paracetamol / acetaminophen.

7. Willing and able to comply with the study requirement.

Exclusion Criteria*:*

1. Pregnant or lactating or planning to become pregnant during the study period.

2. X ray showing evidence of OA with Kellgren-Lawrence grade 4 disease.

3. History of OA pain in the contalateral knee requiring medication (OTC or prescription) within 1 year prior to screening.

4. After discontinuing all pain medications for at least 7 days, has a baseline score of >20 mm on a 0-100 mm Visual Analogue Scale (VAS) for the contalateral knee immediately prior to randomization.

5. History of secondary OA, rheumatoid arthritis, chronic inflammatory disease (e.g. Colitis) or fibromyalgia.

6. History of asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease.

7. History of gastrointestinal bleeding or peptic ulcer disease.

8. Use of warfarin or other anticoagulant therapy within 30 days of study randomization.

9. Elevated transaminases at screening (AST or ALT more than 2 times the upper limit of normal at screening visit).

10. Use of ACE inhibitors, cyclosporine, diuretics, lithium or methotrexate, within 30 days of study randomization.

11. Concomitant use of corticosteroids (any formulation) or use within 30 days of study randomization.

12. Concomitant acetylsalicylic acid therapy other than a stable low dose use of cardiac prophylaxis (max 162 mg daily) taken for at least 3 months prior to enrolment and maintained throughout the duration of the study.

13. Known allergy to aspirin or NSAIDS.

14. Any other acute or chronic illness that in the opinion of the Investigator could compromise the integrity of study data or place the subject at risk by participating in the study.

15. Receipt of any drug as part of a research study within 30 days prior to screening.

16. Previous participation in the study.

17. Any use between screening and baseline of a treatment or medication that may potentially confound study assessment (e.g. use of topical analgesics or anti-anti-inflammatory drugs).

18. Recent history of major knee injury or surgery.

19. Known history of positive HIV.

Adult subjects (male and female) were aged >35 years. All the subjects presented with a clinical diagnosis of OA of the knee according to the American College of Rheumatology (ACR) criteria, including (a) symptoms for at least 6 months prior to screening. (b) Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as buritis, tendonitis, etc) and (c) The pain in the target knee required the use of NSAIDS or paracetamol/acetaminophen (topical or oral treatments).

Approximately 1431 subjects were screened in order to randomize 1176 subjects. The randomized subjects were enrolled in a 1:1:1 ratio and a total of 882 subjects were expected to complete the study. The enrolment continued until approximately 882 subjects completed the study.

Subjects were instructed to apply 4 gm of either test product, or reference product or vehicle to the target knee four times daily for 4 weeks. Subjects were provided with detailed application instructions and a dosing card to standardize the amount applied. The date and time of application were also recorded in subject's diary.

Subjects who were meeting all entry criteria were randomized at baseline visit (Day 0). All study medications (4 gm of either test product, reference product, or vehicle) were self-administered to the treated knee four times daily for 4 weeks. The use of paracetamol /acetaminophen (up to four grams per day) was permitted as rescue therapy for residual knee or other body pain throughout the treatment period.

Subjects were required to use subject diaries in order to record the date and time of study treatments any missed treatment, rescue medication use, and occurrence of adverse effects or in tolerability to study medication. There were a total of 4 study visits. Visit 1/ Screening (Day - 7), Visit 2/baseline /randomization (Day 0), Visit 3/on therapy (week 2) and Visit 4/End of treatment (week 4).

Results:

1176 patients got randomized whereas 882 completed the study after successfully allocating them in three arms in ratio 1:1:1. Age and gender matching was done to ease the comparison. There was a significant improvement in WOMAC pain score over 3 visits (0,2,4 weeks). 1% diclofenac gel showed comparable results against Volteran gel (Table 1). Drug was relatively safe with no reported AEs or SAEs in either arm. (Table 2).

WOMAC pain score at different visits	1% Diclofenac Sodium gel (Generic)	Volteran gel	Placebo
Day 0	5	5	5
2 weeks	3	2	4
4weeks	1	1	4

(1:none; 2:mild pain; 3:moderate pain; 4:severe pain; 5: extreme pain)

Table 1: Showing efficacy of 1% diclofenac sod gel against Volteran gel and placebo

Adverse Event Category	1% Diclofenac Sodium gel(Generic)	Volteran gel
Serious Adverse Events (SAE)		
Cerebrovascular thrombosis SAE	NR	NR

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Coronary thrombosis SAE	NR	NR
GI SAE	NR	NR
Withdrawal due to AEs		
GI WDAE	NR	NR
CVS WDAE	NR	NR
Other WDAE	NR	NR
Non serious AEs		
Dermal AE/Dermatitis	6.5%	3.5%

(SAE: Serious Adverse Events; WDAE: Withdrawal due to Adverse Event; NR: Not Reported)

Table 2: Showing safety profile of 1% diclofenac sod gel against Volteran gel.

Discussion:

Although, pharmacokinetic studies have not been identified for the diclofenac sodium formulation, the similar formulation of diclofenac 1.18% diethylamine salt (equivalent to 1% diclofenac sodium) has been studied extensively.[13] After topical application of 14C-diclofenac diethylamide gel to guinea pigs, maximum blood concentration (Tmax) of radioactivity was reached within 6-8 hours. Steady state blood concentrations were obtained after 3 days of twice daily applications.[14] The distribution of Diclofenac form gel formulation occurs in concentration gradient manner in tissues near the application site to more distal tissues. In pregnant animals, diclofenac crosses the barrier compared metabolism of diclofenac in and the radioactivity is detected in fetuses.[15]

In humans, a pharmacokinetic study demonstrated that systemic NSAID exposure with DSG is minimal: overall systemic exposure to diclofenac when topical DSG was applied to 1 knee was lower, and peak plasma levels were 150-fold lower compared with the standard dose of oral diclofenac the treatment of osteoarthritis (OA). Diclofenac sodium gel 1% had a minimal effect on platelet aggregation, and levels of cox-1 inhibition were much lower than with oral diclofenac and proportional to the topical dose.[16,17]

Diclofenac sodium gel 1% application suppressed COX-2 appreciably, even at the lower diclofenac sodium gel 1% dose. DSG was safe and effective in relieving pain and improving function in randomized, double-blind, controlled trials of 8 weeks duration in patients with hand OA and 12 weeks duration in patients with knee OA. DSG was found to be statistically significantly superior to placebo with respect to all three co-primary endpoints of pain, function and patient global assessment of treatment.[18]

Systemic as well as dermal toxicity studies have been performed with topical diclofenac sodium in multiple animal species. No significant toxicological concerns arose from the dermal toxicology and photo toxicology studies.

The safety data from the short-term controlled and longer-term open-label studies suggest that treatment with diclofenac sodium topical gel is primarily associated with application site reactions, of which application site dermatitis is the most common. Application site reactions were the most frequent reason for treatment discontinuation. Most adverse reactions to diclofenac sodium topical gel were non-serious. With respect to NSAID-related events, the data do not show that patients treated for up to one year with DSG experienced clinically concerning cardiovascular, gastrointestinal, renal, or hepatic reactions.[19,20]

Limitations of study:

As it was a single centre study the results cannot be genralized to entire population. Furthermore comprehensive and multicentric studies including meta analysis of various earler studies should be done, to have a more meaningful and high impact results.

Conclusion:

In summary, Diclofenac sodium topical gel combines low systemic toxicity exposure to diclofenac with effective analgesia and potential tolerability benefits for adult patients with OA pain regardless of age. The gel presents a favourable risk/benefit profile for the treatment of OA.

Acknowledgement:

We extend our sincere thanks to Dr.Abhishek Arun (MD) for his assistance in medical writing. We are also thankful to junior doctors and staff of MV Hospital and Research Centre, Lucknow. Special thanks to everyone who participated in the study.

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