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Review Article

A REVIEW ON EFFECT OF TOPICAL DICLOFENAC FOR RELIEVING THE SYMPTOMS OF OSTEOARTHRITIS

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ABSTRACT

Topical nonsteroidal anti-inflammatory medications (NSAIDs), such as topical diclofenac, have been shown in multiple head-to-head trials to be more effective than oral NSAIDs. They show improve analgesia, give at least similar analgesia, Improvement in physical function and less systemic side effects as compared to oral NSAIDs. Even though efficacy of topical diclofenac in osteoarthritis is well established, understanding of the time it takes for start working, duration of action, And the effective minimum concentration is limited. In case of topical preparations, the concentration in the joint tissues are more likely to be important than concentration in the blood. Recent studies indicate that a decrease in inflammatory markers could be a more accurate predictor of efficacy than plasma concentrations. This narrative review examines the current evidence in these areas and point out where more research and investigation is needed. As a result of our research, topical NSAIDs like diclofenac should be often regarded as a guideline-supported first-line therapy for OA in the knees and hands, particularly for Individuals over the age of 65 and those with concomitant conditions and risk of developing adverse events with oral NSAIDS at high doses.

INTRODUCTION

Approximately 300 million people worldwide suffer from osteoarthritis (OA). Since there are established risk factors for OA such as obesity and increasing age, its prevalence rate, and burden of disease caused by OA is expected to be high.

OA is a complex disease with a wide range of symptoms and eventually leads to degenerative joint disease. OA affects the structure of the body, and it is a type of arthritis that causes cartilage loss and degeneration of the affected joints. Some of the preclinical studies indicates that aberrant stress in the affected joint is turned into intracellular activation. It leads to downstream signalling, resulting in overexpression of inflammatory mediators like prostaglandin, chemokines, and cytokines. As a result, OA is considered as an inflammatory arthritis.

Pain is caused by OA-related joint degeneration and inflammation, which leads to functional restrictions and increased healthcare resource utilisation and patients' diminished quality of life. There are national and international guidelines for management of OA, in that 19 out of 24 guidelines suggests the use of topical NSAIDs as a treatment option for Pain from osteoarthritis. The most recent guideline in this category is the 2019 American College of Rheumatology (ACR) and Arthritis Foundation guideline for management OA suggests topical nonsteroidal anti-inflammatory drugs (NSAIDs) for knee OA, conditionally advises them for the treatment of OA in the hands The topical diclofenac is works by inhibiting the cyclooxygenase – 2 enzyme which are responsible for the conversion of arachidonic acid to prostaglandins, thromboxane and prostacyclins. Thus, it decreases the production of prostaglandin thereby reducing the peripheral pain sensation. In this review, we look at studies on the efficacy, tolerability, and pharmacokinetic/pharmacodynamic properties of topical diclofenac in OA and find out areas where more investigation is required

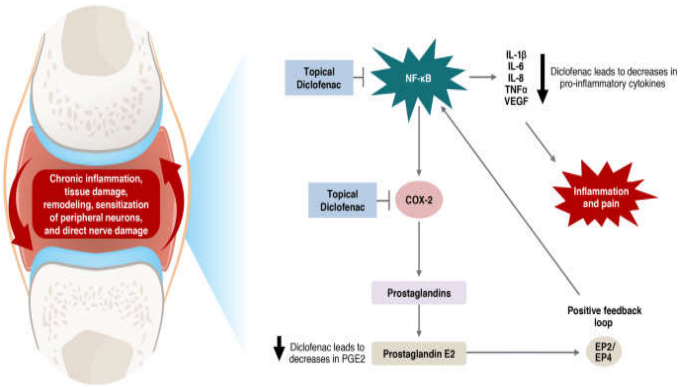

Figure 1 Diagrammatic representation on mechanism of action of topical diclofenac.

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METHODS

We conducted three literature analysis regarding the widespread efficacy of topical diclofenac in OA. It provides information related to the onset of action, duration of action and minimum effective concentration that give analgesic effect.

English-language trials were included in the search of efficacy of topical preparations in OA, specifically in the areas like pain relief. PubMed was used for such trials without any date restrictions on October 24, 2018. Following that, a similar search was undertaken to include safety outcomes of topical diclofenac in OA patients systematic reviews, meta-analyses, and professional guidelines on OA were used in this search.

The onset/duration of action investigation was restricted to English-language clinical studies of oral or topical diclofenac in adults with diverse pain states that reported commencement of action or post dose effectiveness duration. On October 10, 2018, a PubMed search was run with no date limitations. Only studies of topical diclofenac in OA were included in the search results.

Clinical studies of either oral or topical diclofenac in adults with any pain-related condition that reported plasma/serum or tissue concentrations of diclofenac along with an efficacy measure of pain relief or an indirect measure such as reduction of biomarkers included in the MEC search. Without any, date constraints the search were conducted on October 4,2018 using PubMed and by Embase on January 29, 2019.

The authors then added publications based on their knowledge of the field to all of the search categories, and additional references were discovered by cross-referencing publications. This review article is purely based on previously published research and there is no unpublished original data from any of the authors' human or animal studies.

Clinical Evidences for the Safety and Efficacy of Topical Diclofenac In Osteoarthritis Efficacy

The efficacy of topical diclofenac in relieving the chronic pain experienced by the patients with the condition of osteoarthritis have been proved with the support of various systematic reviews and meta-analyses. Recent studies regarding the knee osteoarthritis have also shown the dominance the topical diclofenac over the placebo for pain management. The usage of topical applications of diclofenac like solutions, gel and patches have shown both pain relief as well as functional improvement.

A recently conducted systematic review by Wiffen *et al* claimed clinical success in about 59% of people treated with topical diclofenac gel or solution and 48% in those treated with placebo in patients with knee or hand osteoarthritis.

Tugwell *et al* conducted a RCT in patients with symptomatic knee OA in order to compare the topical solution and the oral capsules of diclofenac. It was a 12-week double- blind double-dummy study. Among the 622 study participants, topical solution of diclofenac (50 drops TID for 12 weeks) has been given to half of its participants (n=311) and the remaining half received oral diclofenac capsules (n=311, 50 mg capsules TID). The statistical results are shown in table 1 and as per the results, similar rates of improvement have been seen in both topical and oral diclofenac.

A RCT conducted by Simon *et al* involved the comparison of five treatments in a total of 775 participants (a) topical diclofenac solution plus oral placebo (n=154), (b) DMSO plus oral placebo (n= 161), (c) topical and oral placebo (n=157), (d) oral diclofenac slow release tablet plus oral placebo (n=151), (e) topical diclofenac solution plus diclofenac tablets (n=152). It was also a 12-week double-blind double-dummy study which involved patients with knee OA. The treatment regimen given was 40 drops of study solution QID and 100 mg slow release tablet daily.

Zacher *et al* conducted a RCT 3 week (21 days) double-blind double-dummy study on 321 patients with OA affecting at least 3 finger joints. In this study, they compared the topical diclofenac diethylamine gel with oral ibuprofen. 165 participants received 10 cm ribbon of gel QID and 156 participants received 400 mg ibuprofen TID for the 21 days. The results of above three RCT are given in the table 1 and as per the results of the three head-to-head studies shows that the topical diclofenac and the oral NSAID provide at least equivalent pain relief in osteoarthritis patients.

Another recently conducted meta-analysis of RCTs in OA which involved seven trials of topical NSAIDs and nine studies of oral NSAIDs states that topical NSAID provides greater reduction in pain (-40.9%) than oral NSAIDs (-34.3%) like acetaminophen, celecoxib and meloxicam. Some evidences suggest that the topical route of administration also contribute to the pain relief, as in one study they compared topical and oral placebo and the pain was found to be reduced to 40% with topical placebo and 29% with oral placebo. Therefore, current evidence indicates that the pain relief achieved by the administration of topical diclofenac is at least similar to some oral NSAIDs.

DEA diethylamine, DMSO diethyl sulfoxide, HAQ Health Assessment Quality of Life, NSAID non-steroidal anti-inflammatory drug, OA osteoarthritis, PBO placebo, PGA patient global assessment, POHA patient overall health assessment, VAS visual analogue scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Safety and Tolerability

Local reactions at the application site (dry skin, redness/erythema, pruritis) are the most common side effects of topical diclofenac, with low systemic effects. In a meta-analysis of topical NSAIDs, increased rates of total adverse events were discovered when compared to topical diclofenac in comparison to placebo in knee studies or hand OA, which is primarily caused by a rise in disorders of the skin and subcutaneous tissues. However, there was no increase in gastrointestinal adverse events and other severe or serious events when compared to placebo.

The main advantage of topical NSAIDs is that they have only limited systemic exposure (e.g., 6.6% absorption of applied dose of 1.5% diclofenac sodium lotion; area under the plasma concentration-time curve from 0 to 24h: mean 233 ng.h/ml with topical administration of 4 g diclofenac sodium gel 1% four times daily vs 3890 ng.h/ml with oral diclofenac sodium 50 mg three times daily for 7 days) compared with oral NSAIDs which have a higher risk of systemic adverse events.

A fewer gastrointestinal events were found by a pooled analysis of two studies comparing the safety of topical diclofenac with that of oral diclofenac in patients with knee

OA (25.4 vs.39.0%, p<0.0001), especially dyspepsia (11.0 vs. 18.4%, p=0.001), diarrhoea (6.5 vs.13.4% p=0.0004), abdominal distension (6.o vs. 10.6%, p=0.01) and upper abdominal pain (5.6 vs. 12.1%, p=0.0005). Topical diclofenac was also linked to a decreased rate of abnormal liver enzyme values at the end of the study when compared with oral diclofenac. Higher rate of dermatological reactions, most commonly dry skin, pruritis, and contact dermatitis were associated with topical administration of diclofenac.

Topical diclofenac offers at least similar analgesia to some oral NSAIDs while causing less systemic adverse events. Adverse events are typically minor and transient local skin reactions. Topical diclofenac is recommended, especially for elderly patients and those who are having comorbid conditions and / or risk factors for various systemic adverse events linked to oral NSAIDs.

Table 1 Studies comparing topical diclofenac and oral NSAIDs for OA pain management

References	Treatment arms	Response measures	Results			
			Pain	Physical function	Stiffness	Other
Tugwell et al.	Diclofenac sodium 1.55 topical solution(n=311) vs. 50 mg oral diclofenac (n=311)	WOMAC pain and Physical function scales, PGA VAS (0-100 mm)	Improved: Topical: 44% Oral: 49% (p=0.23)	Improved: Topical :39% Oral: 46% (p=0.06)	Improved: Topical:39% Oral: 45% (p=0.24)	PGA VAS, Improved: Topical: 43% Oral: 49% (p=0.13)
Simon et al.	5-arm study: 1.Diclofenac sodium 1.5% topical Solution(n=154) Vs. 2.Vehicle (n=161) Vs. 3. PBO (n=157) Vs. 4. 100 mg oral diclofenac(n=151) vs. 5.Diclofenac sodium 1.5% topical solution +100mg oral diclofenac (n=152)	Co-primary efficacyvariables: WOMAC pain, physical function; POHA. Secondary efficacy variables: WOMAC stiffness and PGA	Mean (SD) Change in WOMAC score: Topical: -6.0 (4.5) Vehicle: -4.7 (4.3) Oral: -6.4 (4.1) Topical vs. Vehicle: P=0.009 Topical vs. oral: P=0.429	Mean (SD) Change in WOMAC score: Topical: -15.8 (15.1) Vehicle: -12.1 (14.6) Oral: -17.5 (14.3) Topical vs. Vehicle: P=0.026 Topical vs. Oral: P=0.319	Mean (SD) Change in WOMAC score: Topical: -1.93 (2.01) Vehicle: -1.48 (2.07) Oral: -2.07 (2.02) Topical vs. Vehicle: P=0.035 Topical vs. Oral: P=0.596	Mean (SD) Change: POHA score: Topical: -0.95 (1.30) Vehicle: -0.65 (1.12) Oral: -0.88 (1.31) Topical vs. Vehicle: P=0.956 PGA: Topical: -1.36 (1.19) Vehicle: -1.07 (1.10) Oral: -1.42 (1.29) Topical vs. Vehicle: P=0.018 Topical vs. Oral: P=0.439
Zacher et al.	Diclofenac DEA 1.16% Topical gel (n=165) vs. 400 mg ibuprofen (n=156)	Primary: Response, defined as ≥ 40% improvement in pain Intensity on movement based on VAS Secondary: duration of morning stiffness, grip strength, self-and physician-rated disease activity (100 mm VAS) physician-rated pain on movement (100 mm VAS); HAQ	Response: Topical diclofenac: 44% Oral ibuprofen: 34% P=0.055 Pain at rest, VAS, mean(SD) Change, cm: Diclofenac: -2.00(2.33) Ibuprofen: -2.10(2.06) Pain on movement VAS, mean(SD) change, cm Diclofenac: -2.50(2.04) Ibuprofen: -2.60(1.90)	Grip strength, mean(SD) change, bar: Left hand: Diclofenac: +0.030(0.085) Ibuprofen: +0.020(0.085) Right hand: Diclofenac: +0.023(0.082) Ibuprofen: +0.036(0.093)	Duration of morning stiffness, mean(SD) change, minutes: Diclofenac: -14.5 Ibuprofen: -16.6(23.2)	Disease activity, VAS, mean(SD) change, cm: Self rated: Diclofenac: -2.04(2.22) Ibuprofen: -2.62(2.05) Physician rated: Diclofenac: -2.40(1.96) Ibuprofen: -2.54(1.89) HAQ Diclofenac: -1.6(4.3) Ibuprofen: -2.7(6.8)

In the pooled analysis of the two studies comparing topical and oral diclofenac, demonstrated that cardiovascular adverse events were numerically, but not statistically significantly, lower with topical than oral diclofenac (1.5 vs. 3.5%, p=0.055).

Pharmacokinetic Analysis Onset of action

There are few data on the onset of action of topical Diclofenac. Because of the chronic nature of osteoarthritis, most studies usually focus on long-term effects and are carried out over a long period of time, including some assessment of short-term

effects after treatment. There is only one study that directly assessed the onset of action by hourly assessments in the first few hours after topical Diclofenac application. The study was conducted on patients with knee OA and it is observed that the analgesic effect before diclofenac was detected in plasma on average approximately 4.5 hours after topical application. It suggests that during the interval, diclofenac accumulates in the tissue under the patch, penetrates into muscles, tendons and joint capsules in direct contact with the subcutaneous tissue, which explains the rapid onset of local analgesic without significant concentrations of diclofenac in plasma. Three other studies reported pain score daily after topical diclofenac in patients with osteoarthritis and two collected pain score every 4-7 days in patients with osteoarthritis. Although none of these studies included time to onset of effect as a specific study outcome, benefit was consistently observed sometime within or at the first week of treatment. For clinicians, overall safety and efficacy is very important than onset of action in chronic conditions while onset of pain relief is important in case of patients. Thus it is very important to advise patient that when the medication can be expected to work.

Duration of Effect

For analgesic medications, duration of pain relief is an important consideration. AS the patient is adhered to medicines, it helps to reduce the pain and enhances physical functioning. A double-blind, vehicle-controlled study was conducted in adults with knee OA with 2% diclofenac sodium topical solution applied twice daily and suggested that the twice-daily regimen maintained pain relief. This long-lasting effect may be related to the slower clearance of diclofenac from the inflamed tissue compared to plasma.

Plasma and Synovial Tissue Concentration

The efficacy of analgesic is based on its concentration in synovial compartment. The pharmacokinetic characteristics of diclofenac is different in synovium and plasma. After oral administration, diclofenac will present in inflamed tissue for up to 12 hours with its short plasma half-life of 1-2 hours. This is because of diclofenac's high protein binding capacity, short plasma half-life and hydrophilic/lipophilic polarity. A randomised, double-blind, placebo-controlled crossover study was conducted to comparing the analgesic efficacy of topical (65 mg) and oral (93 mg) diclofenac acid and placebo in reducing inflammatory hyperalgesia from a "freeze lesion'' in ten healthy volunteers. The study suggested that topical diclofenac was more effective than oral diclofenac 1 h after dosing and this efficacy is corresponded to the higher tissue concentrations in the topical group at about 1-1.5 hours. This Diclofenac penetrates inflamed tissue and produces therapeutic activity thereby reduces the pain.

Minimum Effective Concentration

Diclofenac is a strong inhibitor of PGE2 synthesis that has been shown to be 3–1000 times more active than other NSAIDs in inhibiting COX activity on a molar basis. According to Chlud and Wagner in the synovium, diclofenac concentrations of 100–500 ng/ml were commensurate with clinical effectiveness. We previously calculated that a 50% drop in PGE2 would result in an analgesic effect (IC50), it could be obtained by 45 ng/ml of diclofenac in the synovial fluid. Similar studies were conducted by Liauw *et al*, Martel-pelletier *et al* etc and concluded that there is a marginal decrease in PGE2 synthesis with diclofenac. The connection between PGE 2 decrease and analgesia is yet unclear.

Inflammatory cytokines that follow PGE2 in the signal transduction pathway are decreased after exposure to NSAIDs. In the synovial fluid of individuals with OA, the researchers discovered dose-dependent decreases in IL-6, TNFa, and vascular endothelial growth factor. As measuring of inflammatory biomarkers after topical diclofenac is limited these findings are developed from a randomized, open label study of oral NSAIDs including diclofenac 75 mg OD or BID, Ibuprofen 600mg BID or TID etc.

The occurrence of synovitis or effusion has been linked to the development of joint discomfort in people with OA. Pain has also been linked to the presence of pro-inflammatory biomarkers in synovial fluid. In conclusion all these existing evidence based studies of oral diclofenac. Further research is needed before it can be determined whether these concentrations also apply to topical diclofenac.

Challenges in Identifying the MEC

Variability in individual responses to topical diclofenac can be caused by patient and disease-related factors, making it difficult to identify MEC. The stage of OA progression, the varying intensity and nature of inflammation, and the mechanisms behind the patient's pain (inflammatory, nociceptive, and/or central) are all factors contributing to variability in individual responses to topical diclofenac.

The severity of the inflammation, the specific mediators present, and the breadth of the inflammation which central pain systems play a role may differ from one patient to patient and during the course of OA, it's not surprising that the existing, if limited, data on concentrations achieved in various target areas has been variable/inconsistent, and it is difficult to identify MEC of a single diclofenac that would be generally applicable to all OA patients

CONCLUSION

A majority of treatment guidelines recommend using topical NSAIDs, such as diclofenac, to alleviate OA-related joint discomfort. The topical version provided pain alleviation, improved physical function, and reduced stiffness in numerous head-to-head RCTs that were comparable to the oral form. According to a new study, the topical route of administration may improve and enhance analgesic benefits. Pain alleviation begins within a few hours of topical treatment and is often well sustained throughout the 12-hour dosing interval, especially with continued use, according to the study. In OA patients, no unique diclofenac MECs have been found. Distinct biomarkers' concentrations change over time as OA progresses, and the loss of certain biomarkers appears to affect different components of pain sensations in different ways. Topical diclofenac's efficacy in OA is well established, although more study is needed to fully comprehend its effects.

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***Abbrevations**:* OA: Osteoarthritis, NSAIDs: Non-steroidal anti-inflammatory drugs, MEC: Minimum Effective Concentration, IL-6: Interleukin 6, TNFa: Tumor necrosis factor alpha, TID: Three times a day, BID: Two times a day, RCT: Randomized controlled trial

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