Topical Nonsteroidal Anti-inflammatory Medications for Treatment of Temporomandibular Joint Degenerative Pain: A Systematic Review

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Aims: *To evaluate the efficacy of topical nonsteroidal anti-inflammatory drugs (NSAID) to relieve temporomandibular joint (TMJ) degenerative joint disease (DJD) pain.* ***Methods:*** *A search of the literature was made using electronic databases complemented with a manual search. Clinical trials comparing topical NSAID with either placebo or an alternative active treatment to treat TMJ DJD pain were identified. Outcomes evaluated were pain reduction/pain control and/or incidence of side effects.* ***Results:*** *A single study (double-blind randomized placebo-controlled trial) with 20 patients was identified that evaluated the efficacy of a topically prepared NSAID over a 12-week duration, measuring functional pain intensity, voluntary and assisted mouth opening, pain disability index, and a brief pain inventory analysis. This study revealed a pain intensity decrease within treatment groups but no significant difference between treatment groups.* ***Conclusion:*** *Presently, there is insufficient evidence to support the use of topically applied NSAID medications to palliate TMJ DJD pain.* J OROFAC PAIN 2012;26:26–32

Key words: anti-inflammatories, osteoarthritis, systematic review, temporomandibular joint, topical nonsteroidal

Temporomandibular disorders (TMDs) affect the temporomandibular joint (TMJ) and/or masticatory muscles, and approximately 5% to 10% of the population will experience a TMD of significance and seek professional assistance at some point in their lives.[1,2] TMJ degenerative joint disease (DJD) is often referred to as an osteoarthritis (OA), although DJD is only a descriptive term that does not identify etiology[3,4] and is a result of an imbalance between adaptive and nonadaptive responses.

Etiologic factors considered in the pathogenesis of TMJ DJD include trauma (eg, direct blow to the mandible/facial structure) and/or disc derangement/deformation/perforation. Signs and symptoms include pain aggravated by jaw function, decreased joint mobility, joint crepitation, tenderness to palpation of the TMJ capsules, masticatory musculature pain, and radiographic changes of the mandibular condyle, articular fossa, and eminence (erosions, osteophytes, surface flattening, sclerosis).[4–7] With conservative treatment, TMJ DJD is generally self-limiting, with an active (degenerative) phase followed by a reparative (healing) phase; both phases are usually 12 to 18 months in duration.[5–8] Dependent on patient presentation, treatment will range from palliative care to

patient education (ie, an understanding of etiology/pathophysiology), self-care management (eg, soft food diet, eliminating daytime parafunction such as gum chewing, tooth clenching, finger nail biting), physiotherapy to increase joint mobility, utilization of pain medication(s), or occlusal stabilization appliances. Glucosamine sulfate is an adjunctive food supplement that can be recommended as well.[9] At times, intra-articular steroid injections and arthrocentesis will be required for patients refractory to conservative approaches.

Acetaminophen is used for OA pain relief, although its efficacy is reported to be less than that of nonsteroidal anti-inflammatory drugs (NSAID).[10,11] The mechanisms of action of NSAID include the reduction of prostaglandins, thromboxanes, and prostacyclin synthesis via inhibition of one or more isoforms of the cyclo-oxygenase (COX) enzyme system and an analgesic mechanism via inhibition of inflammatory mediators both peripherally and centrally.[12,13]

Oral NSAID are commonly used for OA pain, but long-term use may be associated with adverse side effects including nausea/vomiting, dyspepsia, gastric or duodenal ulceration and bleeding, renal toxicity, increased bleeding time, and increased blood pressure and edema.[13–16]

Topical administration of NSAID has been considered an alternate route for treatment of OA to decrease potential side effects of oral NSAID administration and drug-drug interactions and to treat patients intolerant to oral medications.[10,17,18] Topical preparations include diclofenac sodium, which has been mainly researched for OA of the knee.[18] Pharmacists can compound medications into topical preparations by using various "vehicles" (eg, gels, ointments) with varying degrees of skin penetration. There have been studies with topical NSAID for knee OA pain,[18] although efficacy for TMJ DJD is relatively unknown. The aim of this systematic review was to evaluate the efficacy of topical NSAID to relieve TMJ DJD pain.

Materials and Methods

Search Strategy

A computerized database search was made that included Medline (including in-process and other non-indexed citations, 1950 through week 2 of March 2010), PubMed (1966 through week 2 of March 2010), Embase (1988 through week 2 of March 2010), all Evidence- Based Medicine Reviews (including the Cochrane Database through week 2 of March 2010), and Scopus (1960 through week 2 of March 2010). Key words in the search strategy were: temporomandibular joint or TMJ, temporomandibular disorders or TMD, osteoarthritis, arthritis, joint diseases, NSAID, nonsteroidal anti-inflammatories, topical administration, and diclofenac. The same search strategy was used for each database and there were no language limitations. The combination of search terms used in the different databases is available upon request to the authors. These search terms were selected with the help of a librarian specialized in health sciences databases. The electronic literature search was complemented by a manual search of references of all relevant articles identified. Additionally, studies that fulfilled the inclusion criteria already known by the authors were considered.

Study Selection

Types of Studies. Any type of clinical trial, both prospective and retrospective, randomized and nonrandomized, of patients with TMJ DJD being treated with a topical NSAID and regardless of language was included. Cohort and case-controlled studies were not included.

Types of Participants. All patients with TMJ DJD pain (diagnosed by means of imaging studies correlated with clinical symptoms) regardless of race, age, gender, residential location, or profession were included.

Types of Outcome Measures. The primary outcome was TMJ pain relief/pain control with topical NSAID application. A secondary outcome was minor incidence of side effects. The full-text articles that were selected from the available abstract information were evaluated by each one of the same reviewers to be sure that the selection criteria were actually met. In addition, the quality of the studies was assessed by means of the Instrument to Measure the Likelihood of Bias in Pain Research Reports outlined by Jadad et al.[19]

Results

The electronic and manual database search resulted in five articles being selected that included an MSc thesis dissertation from the University of Alberta, Edmonton, Alberta, Canada (Fig 1). A search of the references of these articles was made by the reviewers and no additional studies were eligible. After applying the selection criteria to the full version of articles selected, four studies were excluded (Table 1) because the topically applied substance used was not an NSAID (eg, capsaicin, methyl salicylate with copper and zinc),[20, 21] a physical

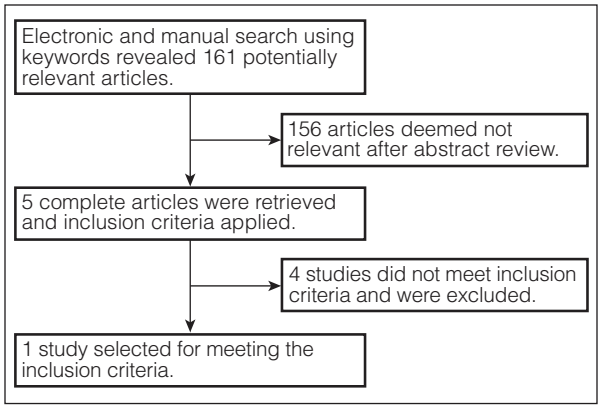

Fig 1 *(left)* Flowchart of systematic review results.

Table 1 Studies Excluded

Study	Reason for exclusion
Di Rienzo Businco et al[23]	Diagnosis was not specified
Lobo et al[21]	Topical substance not an NSAID
Shin and Choi[22]	Phonophoresis (physical means to enhance absorption) used
Winocur et al[20]	Topical substance not an NSAID

means was used to enable NSAID penetration,[22] or the diagnosis of TMJ DJD was not established[23] (attempts were made to communicate with the authors but were unsuccessful).

The lone study selected was a double-blind randomized clinical trial (RCT) on topical diclofenac with efficacy versus placebo for symptomatic relief of TMJ DJD in a 20 patient sample over a total of 12 weeks.[24] Detailed information about this study, which scored 5/5 points according to the Instrument to Measure the Likelihood of Bias in Pain Research Reports,[19] is outlined in Table 2. There was no statistically significant difference in functional pain intensity between the experimental and placebo groups by the end of the study, although a statistically significant difference was found within each group at week 8 (1.677, $P \geq .047$) and week 12 (2.25, $P \geq .003$). There was no statistically significant difference in voluntary and assisted mouth opening between the groups at the end of the study. Various limitations identified by the author included: inadequate sample size that reduced the power of the study to 28%, placebo effect, and potential therapeutic effects of the medication carrier dimethyl sulfoxide (DMSO) used in the treatment placebo (control) group.

Discussion

This systematic review identified only one RCT meeting the criteria for the use of a topical NSAID for treatment of TMJ DJD pain and revealed no statistical difference in pain reduction between the treatment and placebo groups.[24] However, the clinical trial was only for 12 weeks, and the sample size was inadequate to extrapolate results to the general population. In addition, its use of dimethyl sulfoxide (DMSO) may have influenced treatment effect in both the placebo and treatment groups via vasodilatation and/or analgesia and/or anti-inflammatory action. Moore et al[25] had previously suggested that small patient samples can allow for variations in results due to random chance; hence, in order to increase the confidence in the magnitude of the effects of a specific treatment, clinical trial results must provide evidence of relevant successful outcomes as well as involve sample sizes large enough to be representative. Moreover, if the studies were of short duration, they might not have been able to capture accurate results that could represent the different phases of the disease and the real effect of the medication being tested.

Transdermal Drug Absorption

The skin is the largest organ of the body and has been described as a dynamic biomembrane which separates the body from the external environment, a barrier to absorption, and an important route to systemic circulation. The four layers that any given topically applied drug must be transported through include the stratum corneum (external layer), epidermis, basement membrane, and the dermis. The stratum corneum is characterized by its lipophilicity, while the layer underneath, the epidermis, is aqueous. Hence, a drug with both hydrophilic and hydrophobic qualities will be better absorbed by the skin.[17] Due to the skin's natural ability to act as a protective barrier, it becomes a challenge to increase and improve the skin's permeability to certain drugs for therapeutic purposes and to the variety of physical (eg, iontophoresis, phonophoresis) and chemical (eg, DMSO) enhancers and different drug concentrations and preparations (pluronic lecithin organogel, liposome enhanced penetration) that are applied. Nonetheless, transdermal medication absorption offers the advantage of providing local

Table 2 Double-blind RCT on Topical Diclofenac Gel Efficacy Versus Placebo in Symptomatic Relief of TMJ DJD (Wilson[24])

Type of study	Methods	Results	Limitations
Randomized clinical trial; double blind	Sample: 20 female patients between 18 and 45 years old with radiographic evidence of TMJ DJD, pain and tenderness to palpation of the TMJ, baseline score of 30 on a 100-mm VAS. Randomization was computer-generated. Both the examiner and the patients were blinded. -TMJ DJD was diagnosed using a cone beam CT scan evaluated by an oral and maxillofacial radiologist. -Experimental group (12 patients) received 0.2 cc of Pennsaid (1.5% diclofenac + 45.5% DMSO) to be applied topically qid over the TMJ area. Acetaminophen 500 mg (up to 8 tabs/day) was provided for breakthrough pain, if needed. -Placebo group (8 patients) received only DMSO 45.5% to be applied topically over the TMJ area. Acetaminophen 500 mg (up to 8 tabs/day) was provided for breakthrough pain, if needed. -8 patients withdrew from the study (28.6%); 2 from the experimental group and 6 from the control group. -Patients were seen at the initial visit and then every 4 weeks for 12 consecutive weeks. -Functional pain intensity (VAS), voluntary and assisted mouth opening, PDI, and BPI were among the evaluated criteria.	-Pain intensity decreased over time for both groups. -No statistical difference in pain reduction or voluntary/assisted mouth opening between the experimental and placebo groups was found. -Among the reported side effects: burning/itching/peeling/dry skin/paresthesia at the application site, taste alteration. No gastrointestinal side effects reported.	-Small sample. Using 80% power and a 0.05 CI, 26 subjects per group were originally required (calculated via *t* test for Means Power Tables); also, 20% was used as the percentage of possible loss of subjects. In total, the required sample was of 62 subjects. -Moderate duration (12 weeks). -Regression to mean and natural disease progression to be considered. -Conflicting published data suggest that DMSO might have analgesic properties on its own, which could affect study result.

CI = confidence intervals.

therapeutic effects with a decrease in the risk of side effects and toxicity.[26] In order to achieve this, the medication has to reach effective and therapeutic concentrations in the tissues below the application site.[27] This type of medication delivery has been widely used in the medical field for many years (eg, smoking cessation patch, hormone replacement patch, Fentanyl patch, nitroglycerin patch). Patient compliance, drug concentration and formulation, use of enhancers, surface area exposed to the medication, frequency of exposure, and conditions of the skin are some of the many factors influencing the efficacy of the transdermal absorption process.

Equivocal and controversial results have been found regarding peak plasma levels, tissue concentration of a medication underneath the application site, as well as the process through which a topically applied drug reaches a joint and tissues underneath, with the transcutaneous route and systemic distribution after topical application as the probable mechanisms. Rolf et al[28] studied the concentration of ketoprofen in synovial tissues, intra-articular tissues, and plasma in 100 patients undergoing knee arthroscopy after administering a single topical plaster application of ketoprofen (30 mg), multiple topical plaster applications of ketoprofen (30 mg or 50 mg), or ketoprofen administered orally. Results showed high levels of ketoprofen in the synovial fluid after topical administration (70% to 80% of the plasma concentration) and even higher doses of the drug were present in the intra-articular tissues when compared with the levels achieved by oral administration. The synovial compartment has been postulated as an important site of action of NSAID to treat arthritic conditions, directly or through systemic distribution.[27] In another study[26]

in which 20 healthy volunteers participated, two microdialysis probes were inserted into a superficial and a deep tissue layer of the thigh, and diclofenac sodium gel (Voltaren Emulgel, Novartis) strips were applied for a single local dose of approximately 300 mg/100 cm^2 above the site of probe insertion. Effective diclofenac concentrations were attained in 8 of the 20 subjects, whereas in the other 12 there was a complete absence of transdermal penetration. The authors concluded that transdermal penetration of the diclofenac gel may be greatly influenced by individual skin properties, at least after a single application. In a more recent study,[29] 39 healthy volunteers received three different 7-day diclofenac regimes: 16 g topical diclofenac gel 1% (4 g to 1 knee, four times daily); 60 g topical diclofenac gel 1% (4 g to both knees and 2 g to both hands, four times daily); or 150 mg oral diclofenac (50 mg three times daily). Topically applied diclofenac did not inhibit platelet aggregation, and the inhibition of COX-1 and COX-2 enzymes was less than that achieved with oral diclofenac. Also, the systemic exposure achieved after topical diclofenac application was 5 to 17 fold lower than that achieved with the oral diclofenac. Studies by Hui et al[14] and Tanojo et al[30] showed that topically administered diclofenac is not metabolized in the skin, so it is able to perform its action without being immediately inactivated. Although the results of different studies are not consistent, there seems to be some transdermal penetration of a topically applied agent, with varying degrees of concentration of the drug in the tissues underneath and in the synovial fluid and plasma. A diverse group of factors could account for this (eg, skin type, drug concentration, use of enhancers, frequency of application).

Topical NSAID and Hand/Knee OA

Despite the limited evidence for the use of topical NSAID as an alternative treatment for TMJ DJD pain, there is considerable literature available on their use for other joints, with the knee and hand as the most extensively studied. In a quantitative systematic review by Moore et al,[25] a search was performed of RCTs of topically applied NSAID in acute and chronic pain conditions and the results compared with placebo, with other topical NSAID, or with an oral NSAID. Eighty-six reports were found (10,160 patients) that fulfilled the inclusion criteria. In acute (at 1 week) and chronic (at 2 weeks) conditions, topically applied NSAID were found to be significantly superior over the placebo for pain relief (with numbers needed to treat between 3 and 5), along with a low incidence of local/systemic side effects. A meta-analysis of RCTs by Lin et al[31] on the efficacy of topical NSAID in the treatment of OA of the knee, hand, or hip identified 13 RCTs that met their inclusion criteria (1,983 patients) and compared the efficacy of topically applied NSAID to placebo or oral NSAID. The primary outcome measure was reduction in pain from baseline. After topical NSAID application, a reduction in pain and improvement in function and stiffness was superior to placebo during the first 2 weeks of treatment but not in weeks 3 and 4. Lin et al[31] found limited evidence to support the long-term use of topical NSAID to relieve OA pain of the knee, hip, or hand. RCTs of longer duration and larger samples need to be performed in order to evaluate and assess the real effect of topical NSAID in the treatment of knee OA pain.

In a more recent meta-analysis by Bjordal et al[32] on the short-term efficacy of pharmacotherapeutic interventions to treat knee pain due to OA, 63 RCTs with a total of 14,060 patients were evaluated. Treatment groups included: oral NSAID, topical NSAID, intra-articular corticosteroid injections, paracetamol, glucosamine sulphate, chondroitin sulphate, and opioids. Of these, nine trials evaluated the efficacy of a topical NSAID (diclofenac, ibuprofen, eltenac) versus a placebo, in an overall total of 749 patients (with a mean baseline pain of 54.7 mm on a visual analog scale of 100 mm) treated and followed up. Results showed that when treating patients with a topical NSAID for knee OA pain, maximum pain relief was found after 1.6 weeks, with a decrease of 11.6 mm on the scale, as opposed to a reduction of 7.0 mm after 4 weeks. NSAID (either topically and orally administrated) showed values marginally higher than the "minimal perceptible clinical improvement." Moreover, the efficacy of NSAID appeared to decrease gradually after 4 weeks of use, consistent with the Lin et al[31] publication.

In a separate systematic review and meta-analysis[18] of RCTs evaluating Pennsaid (Covidien) for the treatment of OA of the knee, radiographic and clinical features characteristic of knee OA were used to establish the diagnosis; the mean duration of the RCTs was 8.5 weeks. Three RCTs compared Pennsaid to a vehicle control placebo (VCP) (one of these included an additional placebo containing DMSO), while the other RCT compared Pennsaid (50 drops applied in the knee three times/day without rubbing) to oral diclofenac (50 mg three times/day). The dosage of Pennsaid in the VCP RCTs was 1.4 mL (40 drops) applied to only one knee without rubbing four times a day. The criteria used for outcome evaluation included the Western Ontario

and McMaster Universities Arthritis Index (WOMAC) and its subscales (pain, function, and stiffness) and patient global assessment. Three of the four RCTs scored 4.5/5 on the Jadad scale[19]; one unpublished study did not provide sufficient information and could not be adequately evaluated. The results indicated that Pennsaid was statistically better than VCP for the WOMAC index and its subscales. Regarding adverse reactions, subjects in the Pennsaid groups demonstrated a higher risk ratio for minor skin dryness when compared to the VCP groups; the risk ratios for paresthesia and skin rash were similar for both groups, as was that for systemic adverse reactions. When the RCT comparing Pennsaid to oral diclofenac was evaluated, there were no statistically significant differences between them on the WOMAC index and its subscales; oral diclofenac was found more likely to produce gastrointestinal adverse effects, whereas Pennsaid was more likely to produce localized adverse reactions. The results of this systematic review/meta-analysis supported the use of Pennsaid for symptomatic treatment of knee OA and emphasized its safety and efficacy.

Biswal et al[33] published a meta-analysis of RCTs evaluating the long-term efficacy of topical NSAID for knee OA. Only four RCTs met the inclusion criteria. Topical diclofenac and eltenac were the evaluated topical NSAID, and duration of the selected studies varied between 4 and 12 weeks. No statistically significant differences were found between efficacy of the treatment and duration of the study, in contrast to the Lin et al[31] study. Topical NSAID efficacy results were between 35% and 46% when compared with baseline values, with most adverse effects being localized to the application area. It was concluded that topical NSAID are considered effective for the treatment of knee OA, although various details on the methodology, procedure, and outcome measurements, as well as specific statistical information, were not included within the review.

The Osteoarthritis Research Society International, the American College of Rheumatology, the European League Against Rheumatism, and the Third Canadian Consensus Committee suggest that topical NSAID may be considered as an alternate or additional modality for the treatment of knee OA, particularly for patients who prefer topical treatments, are not able to take oral medication, or are at a high risk for complications when using an oral NSAID.[10,34–36] Most published studies have evaluated NSAID topical application for OA of the knee and hand joints. The knee and hand joints, however, offer better application access of topically applied medications (ie, from the front and/or both sides) and have a greater available surface area when compared to the TMJ. The TMJ only allows for lateral topical application over the joint, and this limitation may affect the amount of absorbed medication. In addition, the characteristics of an individual's skin at the application site, age, concentration of the medication, the vehicle used to carry the medication, and the frequency of application need to be considered in future studies. Extrapolation of results from other human joints to the TMJ is far from conclusive at this time. The selected studies in the present systematic review, however, do provide insights for future research. Longer duration and larger RCTs will need to occur prior to definitive recommendations of the use of topical NSAID for the treatment of TMJ DJD pain. Individual variability (eg, skin type, skin hydration, patient compliance), as well as the natural course of the disease, regression to the mean, and placebo effect, need consideration. Currently, there is insufficient evidence supporting the use of a topical NSAID for the treatment of TMJ DJD pain.

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References

1. Temporomandibular disorders. In: de Leeuw R (ed). Orofacial Pain: Guidelines for Assessment, Diagnosis and Management, ed 4. Chicago: Quintessence, 2008:129–204.
2. Al-Jundi MA, John MT, Setz JM, Szentpétery A, Kuss O. Meta-analysis of treatment need for temporomandibular disorders in adult nonpatients. J Orofac Pain 2008;22:97–107.
3. Carlsson GE. Epidemiology and treatment need for temporomandibular disorders. J Orofac Pain 1999;13:232–237.
4. Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: Etiology, diagnosis, and treatment. J Dent Res 2008;87:296–307.
5. Okeson JP. Management of Temporomandibular Disorders and Occlusion, ed 6. St Louis: Mosby, 2008:405–454.
6. Fricton J. Temporomandibular muscle and joint disorders. Pain Clin Updates 2004;12:1–6.
7. Temporomandibular joint pains. In: Okeson JP. Bell's Orofacial Pains, ed 6. Chicago: Quintessence, 2005:329–379.
8. De Bont LGM, Dijkgraaf LC, Stegenga B. Epidemiology and natural progression of articular temporomandibular disorders. Oral Surg Oral Med Oral Pathol 1997; 83:72–76.
9. Thie NMR, Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: A randomized double blind controlled 3 month clinical trial. J Rheumatol 2001;28:1347–1355.
10. Tannenbaum H, Bombardier C, Davis P, Russell AS. An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. J Rheumatol 2006;33:140–157.

11. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomized controlled trials. Ann Rheum Dis 2004; 63:901–907.
12. Hersh EV, Desjardins PJ, Trummel CL, Cooper SA. Nonopioid analgesics, nonsteroidal antiinflammatory drugs, and antirheumatic and antigout drugs. In: Yagiela JA, Dowd FJ, Johnson B, Mariotti A, Neidle EA (eds). Pharmacology and Therapeutics for Dentistry, ed 6. St. Louis: Elsevier Mosby Saunders, 2010:324–358.
13. Lynch ME, Watson CPN. The pharmacotherapy of chronic pain: A review. Pain Res Manage 2006;11:11–38.
14. Hui X, Hewitt PG, Poblete N, Maibach HI, Shainhouse JZ, Wester RC. In vivo bioavailability and metabolism of topical diclofenac lotion in human volunteers. Pharm Res 1998;15:1589–1595.
15. Barkin RL, Buvanendran A. Focus on the COX-1 and COX-2 agents: Renal events of nonsteroidal and antiinflammatory drugs-NSAIDs. Am J Ther 2004;11:124–129.
16. Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee. Arch Intern Med 2004;164: 2017–2023.
17. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. Drugs 1998;56:783–799.
18. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: A systematic review and metaanalysis of randomized controlled trials. J Rheumatol 2006;33:567–573.
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clin Trials 1996;17:1–12.
20. Winocur E, Gavish A, Halachmi M, Eli I, Gazit E. Topical application of capsaicin for the treatment of localized pain in the temporomandibular joint area. J Orofac Pain 2000;14:31–36.
21. Lobo S, Mehta N, Fongione AG, et al. Use of Theraflex-TMJ topical cream for the treatment of temporomandibular joint and muscle pain. Cranio 2004;22:137–144.
22. Shin S-M, Choi J-K. Effect of indomethacin phonophoresis on the relief of temporomandibular joint pain. Cranio 1997;15:345–348.
23. Di Rienzo Businco L, Di Rienzo Businco A, D'Emilia M, Lauriello M, Coen Tirelli G. Topical versus systemic diclofenac in the treatment of temporo-mandibular joint dysfunction symptoms. Acta Otorhinolaryngol Ital 2004;24:279–283.
24. Wilson F. A Placebo Controlled, Double-blind, Randomized Clinical Trial on the Efficacy of Topical Diclofenac for Temporomandibular Degenerative Joint Disease [thesis]. Edmonton: University of Alberta, 2008.
25. Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything: Large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998;78:209–216.
26. Müller M, Mascher H, Kikuta C, et al. Diclofenac concentrations in defined tissue layers after topical administration. Clin Pharmacol Ther 1997;62:293–299.
27. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases. A comparison. Drugs 2000; 60:555–574.
28. Rolf C, Engström B, Beauchard C, Jacobs LD, Le Liboux A. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. Rheum 1999;38: 564–567.
29. Kienzler J-L, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. J Clin Pharmacol 2010;50:50–61.
30. Tanojo H, Wester RC, Shainhouse JZ, Maibach HI. Diclofenac metabolic profile following in vitro percutaneous absorption through viable human skin. Eur J Drug Metab Pharacokinet 1999;24:345–351.
31. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: Meta-analysis of randomized controlled trials. BMJ 2004;329:324–326.
32. Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11:125–138.
33. Biswal S, Medhi B, Pandhi P. Longterm efficacy of topical nonsteroidal antiinflammatory drugs in knee osteoarthritis: Metaanalysis of randomized placebo controlled clinical trials. J Rheumatol 2006;33:1841–1844.
34. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137–162.
35. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–1915.
36. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: An evidence based approach to the management of knee osteoarthritis: Report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Ann Rheum Dis 2003;62:1145–1155.