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CLINICAL FEATURES
REVIEW

Topical therapies for knee osteoarthritis

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ABSTRACT

Background: Symptomatic knee osteoarthritis (OA) involves millions of adults around the world.
Purpose: To analyze the effectiveness and tolerability of topical therapies and their contemporary placement in knee OA management criteria.
Methods: A Cochrane Library and PubMed (MEDLINE) search related to the role of topical therapies in knee OA was carried out.
Results: Many types of local therapy have been reported, including nonsteroidal anti-inflammatory drugs (NSAIDs) like diclofenac and ketoprofen; capsaicin, cream containing glucosamine sulfate, chondroitin sulfate, and camphor; nimesulide; civamide cream 0.075%; menthol; drug-free gel containing ultra-deformable phospholipid vesicles (TDT 064); 4Jointz utilizing Acteev technology; herbal therapies; gel of medical leech (Hirudo medicinalis) saliva extract; and gel prepared using Lake Urmia mud. One systematic review showed that topical diclofenac and topical ketoprofen can alleviate pain. However, another systematic review found that topical diclofenac and ketoprofen had limited efficacy in knee OA at 6 to 12 weeks. Many studies with a low level of evidence have reported some pain mitigation using the rest of aforementioned topical therapies.
Conclusions: Although some controversy exists on the role of topical NSAIDs, current management guidelines advise topical NSAIDs as an option and even first-line therapy for knee OA treatment, particularly among elderly patients. Topical NSAIDs may be contemplated as similar options to oral NSAIDs and are associated with fewer gastrointestinal complications when compared with oral NSAIDs. Caution should be taken with the use of both topical and oral NSAIDs, including close adherence to dosing regimens and monitoring, especially for patients with previous complications of NSAIDs. The role of other topical therapies needs further research.

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Knee; osteoarthritis; pain; topical therapies; NSAIDs

Introduction

Symptomatic knee osteoarthritis (OA) involves millions of adults around the world. Women have a higher predominance of OA, and the risk of developing OA augments with age, obesity, and articular malalignment. OA ordinarily presents with diminished function [1].

Topical therapies have been defined as those designed to act locally, in contrast to transdermal therapies designed to act systemically [2].

Contemporary topical treatments included for the management of knee OA include topical nonsteroidal anti-inflammatory drugs (NSAIDs), capsaicin, and others [3].

This review analyzes the effectiveness and tolerability of topical therapies, their contemporary placement in knee OA management criteria, and their possible role in empowering physicians to provide individualized treatment for their patients with knee OA.

Methods

A Cochrane Library and PubMed (MEDLINE) search related to the role of topical therapies in knee OA was performed. The main criteria for selection were that the articles were focused in the role of topical therapies in knee OA. Regarding eligibility criteria, all types of studies (case study, controlled, uncontrolled, randomized, nonrandomized, reviews, etc.) were considered eligible. Figure 1 shows our search strategies (PubMed/Medline and Cochrane Library). The searches were made since the existence of the search engines (PubMed and Cochrane Library) until 7 July 2018. The only language searched was English.

Results

Current topical treatments included for the management of knee OA are numerous and diverse (Table 1).

Topical nsaids

In a systematic review, Derry et al. stated that topical diclofenac and topical ketoprofen can alleviate pain [4]. However, in another systematic review, Derry et al. found that topical diclofenac and ketoprofen had limited efficacy in knee OA at 6 to 12 weeks [5].

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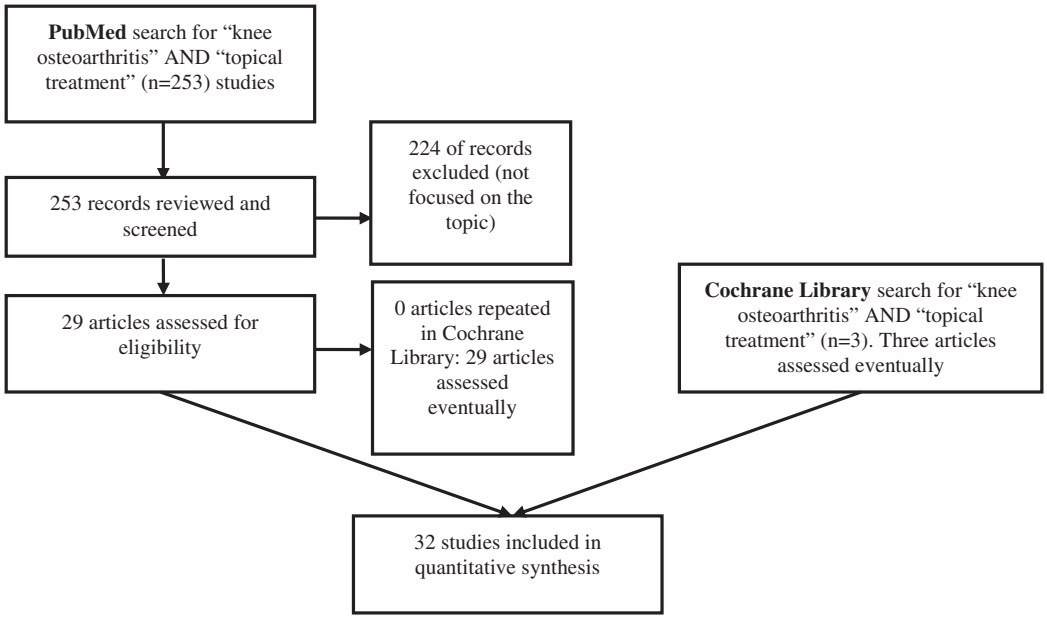

Figure 1. Flow chart of our search strategy regarding the role of topical therapies in knee osteoarthritis.

Table 1. Types of topical treatment of pain in knee osteoarthritis.

NSAIDs
Capsaicin
Cream containing glucosamine sulfate, chondroitin sulfate, and camphor
Nimesulide
Civamide cream 0.075%
Menthol
Drug-free gel containing ultra-deformable phospholipid vesicles (TDT 064)
4Jointz utilizing Acteev technology
Herbal therapies
Gel of medical leech (Hirudo medicinalis) saliva extract
Gel prepared using Lake Urmia mud

In a review article, Meng and Huang found that contemporary treatment criteria advise topical NSAIDs as an option and even first-line therapy for OA management, particularly among elderly patients. Criteria on other topical treatments differ, from advises against their use, to in favor as alternative or coincident treatment, particularly for patients with contraindications to other analgesics [3].

Topical capsaicin

According to Deal et al., 80% of the capsaicin-treated patients accomplished a decrease in pain following two weeks of treatment. It was shown in a double-blind trial on the treatment of OA with topical capsaicin. Transitory burning was perceived at the areas of drug application by about 45% of capsaicin-treated patients; capsaicin cream was considered a secure and effective treatment for knee OA [6]. Seventy patients with OA and 31 with rheumatoid arthritis received capsaicin or placebo for four weeks. The patients were instructed to apply 0.025% capsaicin cream or its vehicle (placebo) to painful knees four times daily.

Kosuwon et al. demonstrated that in knee OA with mild to moderate pain, 0.0125% capsaicin gel was an efficacious treatment [7]. This was a cross-over, double blinded, randomized, controlled trial of 100 patients with mild to moderate knee OA. All of the patients received either capsaicin gel or placebo gel applied to the affected knee, three times daily for 4 weeks with 1-week washout period after which the treatment switched to either capsaicin gel or placebo gel for the next 4 weeks. The only adverse event reported was a burning sensation. During the 4-week treatment with capsaicin, approximately 67% of patients had a burning sensation, but none withdrew for this reason [7].

In a review article, Laslett and Jones observed that topical capsaicin treatment four times daily was well tolerated and moderately efficacious in diminishing pain level up to 20 weeks regardless of area of application and dose in patients with at least moderate pain and clinical or radiological OA [8].

Topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor

Cohen et al. encountered that topical application of glucosamine and chondroitin sulfate was efficacious in alleviating the pain from OA of the knee, and amelioration is obvious within 4 weeks [9]. In this study, 63 patients were randomized to receive either a topical glucosamine and chondroitin preparation or placebo over an 8-week period. Visual analog scale (VAS) scores indicated a greater mean reduction in pain for the glucosamine/chondroitin preparation group compared to the placebo group after 8 weeks.

Topical nimesulide

A study showed that topical nimesulide gel can have beneficial consequences and can ameliorate quality of life in patients with knee OA [10]. Seventy-four adult knee OA outpatients were enrolled in a double-blind, randomized, placebo-controlled study. Treatment group received topical nimesulide gel 1% on the knee skin three times a day, whereas placebo group received an identical-appearing gel for 30 days.

There was a significant improvement in the nimesulide treatment group for all parameters studied. The overall Western Ontario and McMaster Universities OA (WOMAC) scores was significantly better than placebo, but physical functioning, stiffness, and pain scales did not reach statistical significance. For the Nottingham Health Profile (NHP) scores, there was an improvement at 'energy level,' 'pain,' 'physical motion,' and 'NHP distress' scores in the treatment group, whereas no improvement was found in the placebo group. Between-group differences were not significant. Both patient and physician satisfaction scores were significantly better in the treatment group.

Topical civamide cream 0.075%

A study demonstrated the effectiveness of civamide cream for up to 1 year of continuous use [11]. Schnitzer et al. conducted a 12-week, multicenter, randomized, double-blind study with a 52-week open-label extension. Patients with OA of the knee received either civamide cream 0.075% or a lower dose of civamide cream, 0.01%, as the control. The three co-primary endpoints in the double-blind study were the time-weighted average (TWA) of change from baseline to day 84 in the WOMAC pain subscale, the WOMAC physical function subscale, and the Subject Global Evaluation (SGE). In the 52-week open-label extension study, the Osteoarthritis Pain Score and SGE were assessed. A total of 695 patients were randomized to receive civamide cream 0.075% (n = 351) or civamide cream 0.01% (control; n = 344) in the double-blind study. Significance in favor of civamide cream 0.075% was achieved for the TWA for all three co-primary efficacy variables: WOMAC pain, WOMAC physical function, and SGE; and at day 84 for these three variables. These analyses accounted for significant baseline-by-treatment interactions. In the 52-week open-label extension, efficacy was maintained. Civamide cream 0.075% was well tolerated throughout the studies.

Topical menthol

A study provided incomplete support concerning the effectiveness of menthol gel to ameliorate functioning and diminish pain among patients with knee OA [12]. In this study, Topp et al. analyzed 20 individuals with knee OA. Individuals volunteered to complete two data collection visits 1 week apart. Subjects underwent the same data collection at each visit including the performance of functional tasks and self-reporting knee pain while performing each task. The functional tasks included a 6-Minute Walk (6-MW), the Timed Get Up and Go (TUG), 30-second timed chair stand (TCS), and time to ascend (Up stairs) and descend (Down stairs) a flight of stairs. Subjects reported their knee pain immediately following each functional task using a 100-mm visual analog scale. These assessments of pain and functioning were measured twice at each subject visit: upon arrival at the facility without any intervention and again during the same visit after random application to the OA knee of 5 mL of 3.5% menthol gel or 5 mL of an inert gel. There were no significant between-group differences or time by treatment interaction in performance of any of the functional tasks, or measures of pain, at any of the data collection time points. However, there were significant within-group differences. Scores on the 6-MW, TCS, and Down stairs functional tasks improved significantly following the application of menthol gel. Scores on the Down stairs functional task improved significantly following application of the placebo gel. The menthol intervention resulted in significant reductions in pain during the TUG, TCS, Up stairs, and Down stairs tasks. The placebo condition did not result in any significant changes in pain during the functional tasks. No differences were detected in functional tasks or pain following the placebo and menthol conditions [12].

Drug-free gel containing ultra-deformable phospholipid vesicles (TDT 064)

In a review article, Conaghan et al. revised the role of TDT 064, a drug-free, topical gel containing ultra-deformable phospholipid vesicles (Sequessome * vesicles), for knee OA pain. Evidence from reported studies supported the use of TDT 064 as a topical treatment for patients with knee OA [13].

Topical 4Jointz utilizing Acteev technology

Laslett et al. evaluated the effectiveness of thrice daily topical 4Jointz using Acteev technology (a combination of a standardized comfrey extract and a pharmaceutical grade tannic acid, 3.5 g/day) on OA knee pain over 12 weeks. Topical 4Jointz diminished pain [14]. In this study, adults aged 50–80 years (n = 133) with clinical knee OA were randomized to receive 4Jointz or placebo in addition to existing medications. Pain and function were measured using a VAS and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scale at baseline, 4, 8, and 12 weeks. Inflammation was measured analyzing IL-6 expression and CTX-2 presence as representative for cartilage breakdown using ELISA, at baseline and 12 weeks. Pain scores significantly reduced in the group who received 4Jointz compared to the group who received placebo after 12 weeks using both the VAS and the KOOS pain scale. Changes in IL-6 and CTX-2 were not significant. Post-hoc analyses suggested that treatment may be most effective in women and those with milder radiographic OA. Rates of adverse events were similar in both groups, excepting local rash that was more common among participants receiving 4Jointz (21% vs 1.6%), but only 26% (n = 4) of participants with rashes discontinued treatment. There were no changes in systemic blood results [14].

Topical herbal therapies

In a systematic review reported by Cameron and Chrubasik on the role of topical herbal therapies for treating knee OA, they stated that *Arnica* gel possibly ameliorates symptoms as effectively as a gel containing NSAIDs, but with no better (and possibly worse) complication profile. Comfrey extract gel possibly ameliorates pain, and *Capsicum* extract gel will not possibly ameliorate pain or function at the doses analyzed in this report [15].

Topical application of Arnica montana fresh plant gel, applied twice daily, for 6 weeks proved to be a secure, well-

tolerated, and efficacious treatment of mild to moderate OA of the knee [16]. Knuesel et al. performed an open multicenter trial and investigated the safety and efficacy of an Arnica montana fresh plant gel, applied twice daily, in 26 men and 53 women with mild to moderate OA of the knee. After 3 and 6 weeks, significant decreases in median total scores on the WOMAC were evident in the intention-to-treat and per-protocol populations. Scores on the pain, stiffness, and function subscales also showed significant reductions at these time-points. The overall local adverse-event rate of 7.6% included only one allergic reaction. Sixty-nine patients (87%) rated the tolerability of the gel as 'good' or 'fairly good,' and 76% would use it again [16].

A pilot study concluded that topical treatment with Sambucus ebulus L. (S. ebulus) gel can be advised for improving symptoms of patients with knee OA [17]. Jabbari et al. analyzed 79 patients with knee OA. They were randomly enrolled in two parallel arms of a pilot randomized, double-blind, active-controlled clinical trial. The patients were treated by topical S. ebulus gel or 1% diclofenac gel, three times a day, as much as a fingertip unit for 4 weeks. Patients were assessed prior to enrollment and, then, 2 and 4 weeks subsequent to the intervention, in terms of scores of VAS for self-grading of their knee joint pain, and according to three different domains of WOMAC questionnaire. Any observed adverse effects were also scrutinized. The mean values of WOMAC pain score, total WOMAC score, and VAS score for pain of the S. ebulus group were significantly lower compared with the diclofenac group. In addition, no serious adverse effect was reported.

Patients with knee OA at phases II to III (Kellgren-Lawrence) were randomly allocated to 4 weeks of treatment with cabbage leaf wraps (CLWs) (daily for at least 2 hours), topical pain gel (TPG) (10 mg diclofenac/g, at least once daily), or common care (UC). CLWs were more efficacious than UC, but not compared with TPG. Therefore, CLWs might be advised for patients with knee OA [18]. Lauche et al. studied 81 patients (42 women, 65.9 ± 10.3 y). After 4 weeks, patients in the CLW group reported significantly less pain compared with those in the UC group but not when compared with the TPG group. Significant effects were also found in WOMAC, SF-36, 30-second Chair Stand Test, and PPT scores in the CLW group compared with the UC group. Compared with TPG, effects from CLW were found for WOMAC after 4 weeks and for quality of life after 12 weeks. Patients were satisfied with both active interventions, and except for two adverse events in both groups, the applications were well tolerated [18].

Topical gel of medical leech (Hirudo medicinalis) saliva extract

In patient with knee OA, leech saliva extract (LSE) in the liposome-based gel alleviated pain up to 50% [19]. Shakouri et al. used LSE as a supplementary treatment to relief the signs and symptoms of OA. The saliva of medical leech was extracted, and nano liposomes were used to formulate the supplement to enhance skin absorption. A clinical trial was designed to evaluate the therapeutic effects of LSE liposomal gel. Lenquesne and VAS questionnaires were used as indexes of this supplement therapy efficacy for 30 days. Questionnaires analysis showed that after one-month administration of LSE liposomal gel, patients' pain was relieved approximately up to 50%; also, due to reduction in joint inflammation and stiffness, the range of motion was increased, and the patients' quality of life was enhanced. LSE nano-scaled liposomal gel, as an innovative supplement therapy in OA patients, makes desirable therapeutic approach, which seems to make a significant impact on patient's quality of life and self-care capability [19]

Topical gel prepared using Lake Urmia mud

Mud therapy (Lake Urmia mud for topical gel formulation) was efficacious in knee OA treatment and pain reduction [20]. Mahboob et al. analyzed 50 patients suffering from knee OA. Patients were randomized into two groups: case group and control group. Patients in the case group received mud therapy, and the placebo was applied to patients in the control group. Three parameters including pain, morning stiffness, and joint functionality were assessed in all patients. VAS and WOMAC were the employed scales for pain assessment. Functional capacity was evaluated by using WOMAC functional capacity and WOMAC global index. All the mentioned steps were done before and after treatment. Blood samples, in both groups, were collected for measuring tumor necrosis factor (TNF)-alpha serum level. All the differences (for three parameters), in the case group, were statistically significant. TNF-alpha serum level reduction in both groups were detected: 19.41% in the case group and 1.76% in the control group [20].

Discussion

NSAIDs are pillars of the treatment of OA [21]. However, they have dose- and age-related risks of gastrointestinal, cardiovascular, and renal complications. Therefore, US and international guidelines advised caution when prescribing oral NSAIDs, especially in older patients and those with important comorbidities [21].

Pharmacologic therapy of symptomatic knee OA is principally limited to analgesic and anti-inflammatory drugs. Usually, topical drugs or paracetamol are advised as first-line therapies. If they fail, oral NSAIDs or COX-2-selective inhibitors should be indicated. Tramadol is an alternative in the case patients will not react adequately to NSAIDs. The use of glucosamine and chondroitine sulfate is still controversial in knee OA. Oral NSAIDs should be indicated with caution due to possible complications. Opioids are not advised as their benefits are outweighed by an augmented risk for severe complications [22].

Bruyere et al. advised a mixed pharmacological and non-pharmacological treatment with some initial measures, including information access/education, weight loss if overweight, and an adequate exercise program [23]. Altman et al. advised topical NSAIDs, indicating them as a secure and efficacious treatment. One guideline advised that topical NSAIDs should be considered as first-line pharmacologic therapy. A US guideline advised topical NSAIDs in older patients and in patients

with augmented gastrointestinal risk. The consensus across US and European OA guidelines was that topical NSAIDs were a secure and efficacious treatment for knee OA [1].

Klinge and Sawyer studied the effectiveness and safety of topical versus oral nonsteroidal anti-inflammatory drugs in a comprehensive review. These authors stated that topical NSAIDs are created to aim their therapeutic effect locally to painful areas while lessening systemic exposure [24]. In comparative studies, topical and oral NSAIDs performed significantly better than placebo for chronic injury treatment. However, topical and oral NSAIDs showed analogous effectiveness for treatment of chronic injuries. There were more gastrointestinal complications in patients taking oral NSAIDs, while local skin reactions happened more commonly in patients treated with topical NSAIDs. Overall, topical NSAIDs may be contemplated as similar options to oral NSAIDs and are associated with fewer gastrointestinal complications when compared with oral NSAIDs. Caution should be taken with the use of both topical and oral NSAIDs, including close adherence to dosing regimens and monitoring, especially for patients with previous complications of NSAIDs [24].

According to Rannou et al., topical NSAIDs are advised in international and national guidelines as an early treatment alternative for the symptomatic management of knee OA, and they may be utilized ahead of oral NSAIDs due to their superior security profile [25]. Topical NSAIDs have a moderate effect on pain mitigation, with effectiveness analogous to that of oral NSAIDs, with the advantage of a better risk:benefit ratio. Topical and oral NSAIDs have shown a similar effect on knee pain over 1 year of treatment, with fewer complications due to lower systemic absorption of topical NSAIDs compared with oral NSAIDs. Consequently, topical NSAIDs may be the preferred treatment alternative, particularly in OA patients aged ≥ 75 years, and those with co-morbidities or at an augmented risk of cardiovascular, gastrointestinal, or renal complications [25].

Meng and Huang have reported that current management guidelines advise topical NSAIDs as an option and even first-line therapy for OA treatment, particularly among elderly patients [3]. Guidelines on other topical treatments differ, from recommendations against their use, to in favor as option or coincident therapy, particularly for patients with contraindications to other pain killers. Although frequently well tolerated and chosen by many patients, clinical care still lags in the adoption of topical therapies. Aspects of effectiveness, security, and patient quality of life data need further investigation [3].

Future prospects for topical or transdermal OA treatments included new technologies in permeation promoters and nanotechnology [26–32]. Azzizi et al. have recently reported that the size of the emulsion particles is an important factor in topical drug delivery systems. Almond oil (oil phase) was mixed with Tween 80 and Span 80 (surfactants) and ethanol (co-surfactant), and distilled water (aqueous phase) was then added to the mixture at once. Prepared nanoemulsions were pre-emulsified into a 100 ml beaker using magnet/stirrer (1000 rpm). Then, utilizing a probe ultrasonicator (Hielscher UP400s, Hielscher, Ringwood, NJ), the nanoemulsions were formed. The optimized nanoemulsion formulation containing 2.5% ibuprofen showed better analgesic and anti-inflammatory effects than commercial product and corresponding microemulsion product containing 5% ibuprofen (i.e. twice the content of ibuprofen in the nanoemulsion) *in vivo*. The nanoemulsion preparation showed better analgesic activities during chronic phase. Also, it reduced the swelling from the first hour, while the microemulsion and the commercial product began to demonstrate their anti-inflammatory effects after 2 and 3 hours, respectively.

In conclusion, topical NSAIDs have a moderate effect on pain mitigation, with effectiveness similar to that of oral NSAIDs, with the advantage of a better risk:benefit ratio. One study showed that topical and oral NSAIDs have a similar effect on knee pain over 1 year of treatment, with fewer complications due to lower systemic absorption of topical NSAIDs compared with oral NSAIDs. Consequently, topical NSAIDs may be the preferred treatment alternative, particularly in OA patients aged ≥ 75 years, and those with comorbidities or at an augmented risk of cardiovascular, gastrointestinal, or renal complications. I do believe that the results of this research can contribute to the physician's clinical practice in the management of knee OA.

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Declaration of interest

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