1 Initial Treatment of Knee Osteoarthritis: Oral and Topical Drugs

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1.1 Introduction

Osteoarthritis (OA) is a frequent cause of knee pain. There are a number of conservative treatments of knee osteoarthritis (KOA) that must be used before indicating surgical treatment. The purpose of this chapter is to analyze the existing conservative strategies for the treatment of pain related to KOA.

1.2 Oral Drugs

1.2.1 Acetaminophen

Published guidelines and expert opinion are divided over the relative role of acetaminophen (also called paracetamol or Tylenol) and non-steroidal anti-inflammatory drugs (NSAIDs) as first-line pharmacologic therapy of KOA. The comparative safety of acetaminophen and NSAIDs is also important to consider. In a systematic review Towheed et al. [1] evaluated the efficacy and safety of acetaminophen versus placebo and versus NSAIDs (ibuprofen, diclofenac, arthrotec, celecoxib, naproxen, rofecoxib) for treating KOA. Their findings suggested that NSAIDs were superior to acetaminophen for improving knee and hip pain in people with KOA. In KOA patients with moderate-to-severe levels of pain, NSAIDs appeared to be more effective than acetaminophen.

1.2.2 Tramadol

Tramadol is increasingly used for the treatment of KOA because, in contrast to NSAIDs, tramadol does not produce gastrointestinal bleeding or renal problems, and does not affect articular cartilage. Cepeda et al. [2] sought to determine the analgesic effectiveness, the effect on physical function, the duration of benefit, and the safety of oral tramadol in people with KOA. Tramadol or tramadol/paracetamol decreased pain intensity, produced symptom relief, and improved function, but these benefits were small.

In 2019, Toupin April et al. reported a systematic review to determine the benefits and harms of oral tramadol or tramadol combined with acetaminophen or NSAIDs in patients with KOA [3]. Moderate quality evidence indicated that compared to placebo, tramadol alone or in combination with acetaminophen probably has no important benefit on mean pain or function in patients with OA, although slightly more patients

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in the tramadol group report an important improvement (defined as 20% or more).

1.2.3 Oral Opioids

Opioids may be a viable treatment option if patients with KOA suffer from severe pain or if other analgesics are contraindicated. However, the evidence about their effectiveness and safety is contradictory. Nüesch et al. [4] tried to determine the effects on pain and function and the safety of oral or transdermal opioids as compared with placebo or no intervention in patients with KOA. The small to moderate beneficial effects of non-tramadol opioids were outweighed by large increases in the risk of adverse events. Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe.

1.2.4 Glucosamine

Towheed et al. [5] reviewed all randomized controlled trials evaluating the effectiveness and toxicity of glucosamine in KOA. WOMAC (Western Ontario and McMaster. Universities Osteoarthritis Index) outcomes of pain, stiffness, and function did not show a superiority of glucosamine over placebo. Glucosamine was as safe as placebo.

1.2.5 Diacerein

Diacerein acts differently from traditional NSAIDs which inhibit prostaglandin synthesis, leading to adverse gastrointestinal effects. It has been proposed that diacerein acts as a slow-acting, symptom-modifying, and perhaps disease-structure modifying drug for KOA. Fidelix et al. [6] reported that pain reduction with diacerein treatment was minimal.

1.2.6 Doxycycline

Preclinical data suggest that doxycycline might act as a disease-modifying agent for the treatment of KOA, with the potential to slow cartilage degeneration. Da Costa et al. found that the benefit of doxycycline was minimal to non-existent [7].

1.2.7 Chondroitin Sulfate

Singh et al. [8] have reported that in the short-term chondroitin sulfate (CS), alone or combined with glucosamine, is better than placebo regarding the improvement of pain.

In 2019, Honvo et al. analyzed the role of pharmaceutical-grade CS [9]. They stated that only the pharmaceutical-grade CS may be considered as an appropriate background treatment for the management of KOA. Evidence from another recent meta-analysis, using data from full safety reports, confirms the good safety profile of CS in OA.

1.2.8 Duloxetine

In 2019, Chen et al. reported a meta-analysis of randomized controlled trials on the efficacy and tolerability of duloxetine in patients with KOA. They found that duloxetine is effective in the management of chronic pain and loss of physical function in KOA with acceptable adverse events despite having no advantage in treating joint stiffness [10].

1.2.9 Curcuma Longa

In a double-blind multicenter randomized placebo controlled three-arm study reported in 2019 by Henrotin et al. found that bio-optimized curcuma longa (BCL) extract was efficient on KOA pain [11]. BCL appeared safe and well tolerated with no evidence of severe adverse effects. Efficacy analysis suggested positive trends for measurements of PGADA (Patient Global Assessment of Disease Activity) and serum levels of an OA biomarker and showed a rapid and significant decrease of pain in KOA.

Table 1.1 Types of topical treatment of pain in knee osteoarthritis

Non-steroidal anti-inflammatory drugs (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

1.3 Topical Drugs

Current topical treatments included for the management of KOA are numerous and diverse (Table 1.1).

1.3.1 Topical NSAIDs

In a systematic review Derry et al. stated that topical diclofenac and topical ketoprofen can alleviate pain [12]. However, in another systematic review, Derry et al. found that topical diclofenac and ketoprofen had limited efficacy in KOA at 6–12 weeks [13].

In a review article, Meng and Huang found that contemporary treatment criteria advise topical NSAIDs as an option and even first-line therapy for KOA 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 [14].

1.3.2 Topical Capsaicin

According to Deal et al. 80% of the capsaicin-treated patients accomplished a decrease in pain following 2 weeks of treatment. It was shown in a double-blind trial on the treatment of KOA 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 KOA [15]. Seventy patients with KOA and 31 with rheumatoid arthritis received capsaicin or placebo for 4 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 KOA with mild to moderate pain, 0.0125% capsaicin gel was an efficacious treatment [16]. This was a cross-over; double blinded, randomized, controlled trial of 100 patients with mild to moderate KOA. 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 [16].

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 KOA [17].

1.3.3 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 KOA and amelioration is obvious within 4 weeks [18]. In this study 63 patients were randomized to receive either a topical glucosamine and CS preparation or placebo over an 8 week period. Visual analogue scale (VAS) scores indicated a greater mean reduction in pain for the glucosamine/CS

preparation group compared to the placebo group after 8 weeks.

1.3.4 Topical Nimesulide

A study showed that topical nimesulide gel can have beneficial consequences and can ameliorate quality of life in patients with KOA [19]. Seventy-four adult KOA outpatients were enrolled in a double-blind, randomized, placebo-controlled study. Treatment group received topical nimesulide gel 1% on the knee skin 3 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 WOMAC scores were 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.

1.3.5 Topical Civamide Cream 0.075%

A study demonstrated the effectiveness of civamide cream for up to 1 year of continuous use [20]. Schnitzer et al. conducted a 12-week, multicenter, randomized, double-blind study with a 52-week open-label extension. Patients with KOA 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.

1.3.6 Topical Menthol

A study provided incomplete support concerning the effectiveness of menthol gel to ameliorate functioning and diminish pain among patients with KOA [21]. In this study Topp et al. analyzed twenty individuals with KOA. 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-s 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. There were no differences detected in functional tasks or pain following the placebo and menthol conditions [21].

1.3.7 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 KOA pain. Evidence from reported studies supported the use of TDT 064 as a topical treatment for patients with KOA [22].

1.3.8 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 [23]. In this study adults aged 50–80 years ($n = 133$) with clinical KOA 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 KOA. 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 [23].

1.3.9 Topical Herbal Therapies

In a systematic review reported by Cameron and Chrubasik on the role of topical herbal therapies for treating KOA, 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 possible will not ameliorate pain or function at the doses analyzed in this report [24].

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 KOA [25]. Knuesel et al. performed an open multicenter trial 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 [25].

A pilot study concluded that topical treatment with Sambucus ebulus L. (*S. ebulus*) gel can be advised for improving symptoms of patients with KOA [26]. Jabbari et al. analyzed seventy nine patients with KOA. 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 KOA 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 h), 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 KOA [27]. Lauche et al. studied 81 patients (42 women, 65.9 ± 10.3 years). 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-s 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 [27].

1.3.10 Topical Gel of Medical Leech (Hirudo Medicinalis) Saliva Extract

In patient with KOA leech saliva extract (LSE) in the liposome-based gel alleviated pain up to 50% [28]. 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 nanoliposomes 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 1-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 [28].

1.3.11 Topical Gel Prepared Using Lake Urmia Mud

Mud therapy (Lake Urmia mud for topical gel formulation) was efficacious in KOA treatment and pain reduction [29]. Mahboob et al. analyzed 50 patients suffering from KOA. 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 was detected: 19.41% in the case group and 1.76% in the control group [29].

1.3.12 Buprenorphine Transdermal Patch (BTDP)

In 2019, Gil et al. have stated that after the BTDP application, the NRS (Numeric Rating Scale) score in the knee applied group was lower than that of the chest applied group [30]. NRS scores after buprenorphine patch decreased to 2.21, and

2.55 in the chest applied group and the knee applied group, respectively. The adverse effects were 19.32% in the knee applied group, and 64% in the chest applied group. The compliances were 82.95% and 37.60% in the knee applied group and chest applied group, respectively. This novel application of BTDP directly to the painful knee joint of KOA patients led to a decrease in the NRS score, adverse effects, and an increase in compliance compared with the chest application method.

1.4 Comparative Studies

1.4.1 Curcumin Versus Diclofenac

In 2019, Shep et al. compared the efficacy and safety of curcumin with those of diclofenac in the treatment of KOA [31]. Curcumin had similar efficacy to diclofenac but demonstrated better tolerance among patients with KOA. Curcumin can be an alternative treatment option in the patients with KOA who are intolerant to the side effects of non-steroidal anti-inflammatory drugs.

1.4.2 Gabapentin Versus Duloxetine

Enteshari-Moghhadam et al. have reported in 2019 that gabapentin and duloxetine have similar and acceptable effects in pain reduction and improvement of functional status in patients with KOA at the end of the third month's treatment. Duloxetine effects begin from the first weeks, while gabapentin effects begin gradually with the best at the end of the third month [32].

1.4.3 Thymus Daenensis Gel 5% Versus Diclofenac

According to Dehghan et al. thymus daenensis gel improves the symptoms in patients equal and without significant difference than diclofenac. One hundred and twenty patients were divided into three groups. Patients in each group were treated by 5% Thymus daenensis gel, 1% diclofenac gel, or placebo for 6 weeks, along with oral celecoxib capsules. Patients were assessed in different intervals, based on the VAS score for assessment of pain in the joint and different dimensions of WOMAC questionnaire [33].

1.5 Endorsement by Central European Experts of the Revised ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases) Algorithm for the Management of KOA

According to Kucharz et al., KOA is a chronic disease that requires intervention with both non-pharmacological and pharmacological treatment modalities and, inevitably, disease progression may necessitate successive treatments throughout the course of the disease [34]. There is increasing data on the shortfalls of current pharmacological treatment of KOA, and safety concerns associated with analgesic therapy use in KOA arising from increasing evidence of gastrointestinal, cardiovascular, hepatic, and renal adverse events with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Consequently, symptomatic slow-acting drugs for OA (SYSADOAs) may now be considered as a first-line treatment for KOA, with a particular emphasis placed on the outstanding benefit: risk ratio of pharmaceutical-grade glucosamine and chondroitin sulfate formulations.

1.6 Osteoarthritis Research Society International (OARSI) Guidelines for the Nonsurgical Management of Knee Osteoarthritis

According to Bannuru et al., core treatments for KOA included arthritis education and structured land-based exercise programs with or without dietary weight management [35]. Topical NSAIDs are strongly recommended for individuals with KOA (Level 1A). For individuals with gastrointestinal comorbidities, COX-2 inhibitors

were Level 1B and NSAIDs with proton pump inhibitors Level 2. For individuals with cardiovascular comorbidities or frailty, use of any oral NSAID was not recommended. The use of acetaminophen/paracetamol was conditionally not recommended (Level 4A and 4B), and the use of oral and transdermal opioids was strongly not recommended (Level 5).

1.7 Conclusions

Two main strategies for the conservative treatment of KOA exist: oral and topical drugs. These methods must be used before indicating invasive therapies (intra-articular injections or surgical treatment). Oral drugs have a great importance. NSAIDs have shown to be superior to acetaminophen. The benefits found in tramadol or tramadol/paracetamol, non-tramadol opioids, glucosamine, diacerein, and doxycycline are small.

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 KOA patients aged ≥75 years, and those with comorbidities or at an augmented risk of cardiovascular, gastrointestinal, or renal complications. We do believe that the results of this research can contribute to the physician's clinical practice in the management of KOA.

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KOA is a chronic disease that requires intervention with both non-pharmacological and pharmacological treatment modalities and, inevitably, disease progression may necessitate successive treatments throughout the course of the disease. There is increasing data on the shortfalls of current pharmacological treatment of KOA, and safety concerns associated with analgesic therapy use in KOA arising from increasing evidence of gastrointestinal, cardiovascular, hepatic, and renal adverse events with paracetamol and (NSAIDs). Consequently, symptomatic slow-acting drugs for OA (SYSADOAs) may now be considered as a first-line treatment for KOA, with a particular emphasis placed on the outstanding benefit: risk ratio of pharmaceutical-grade glucosamine and chondroitin sulfate formulations.

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