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Pharmacological treatment of osteoarthritis of the hip and knee

A range of oral analgesics, topical treatments, and intra-articular injections can be used to reduce pain and improve function in patients with osteoarthritis of the hip and knee.

ABSTRACT: Treatment goals for the management of hip and knee osteoarthritis are to reduce pain, maintain or improve function, and, where possible, to slow the progress of the underlying disease. The benefits and potential toxicities of pharmacological options should be considered and treatment should be individualized according to patient symptoms, preferences, and a therapeutic agent's overall safety profile. When intrusive pain or disability persists despite a substantial trial of nonsurgical therapy, or when controlling symptoms requires long-term opioids, high-dose acetaminophen or NSAIDs, and repeated intra-articular injections, referral for surgical options should be considered.

Treatment for hip and knee osteoarthritis (OA) aims to reduce pain, maintain or improve function, and, where possible, to slow the progress of the underlying disease. Although no medication has yet been shown to slow the advance of joint pathology in osteoarthritis, pharmacological management remains an integral component of therapy for most patients in the course of their disease.

Knowledge of the current evidence can support safe and effective counseling and prescribing practices, and assist in determining when to refer for surgery. As well as considering the benefits and potential toxicities of pharmacological options, physicians must individualize treatment based on patient symptoms and preferences.

Glucosamine sulfate and chondroitin sulfate

Glucosamine is one of the most commonly used complementary or alternative medicine products in North America. Typically derived from the ground shells of shellfish or from processed grains, glucosamine has proponents who claim it restores glycosaminoglycans in arthritic joints and reduces pain and inflammation.[1] Evidence for the proposed mechanism is insufficient *in vivo*, but some studies have reported benefits from glucosamine in terms of pain relief and even radiographic progression.[1]

Evidence for a positive effect is controversial, however, with several studies showing no benefit over placebo.[1,2] The Osteoarthritis Research Society International (OARSI) guidelines state that "treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA," but "if no response is apparent within 6 months treatment should be discontinued."[2] Other guidelines, such as those for the American Academy of Orthopaedic Surgeons, make a recommendation that physicians not prescribe glucosamine.[3] Both sets of guidelines are based on level I evidence.[2,3]

This disparity in recommendations is considered to be due to the heterogeneity of existing studies, particularly with respect to adequacy

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of allocation concealment.[2] Little or no benefit has been observed when concealment is adequate.[2] Evidence regarding chondroitin sulfate is similarly inconsistent.[2] There is marked heterogeneity of outcomes between trials, and again higher-quality studies with adequate concealment have been unable to show significant benefit.[1,2]

Overall, the evidence and recommendations remain inconsistent for both glucosamine and chondroitin.[1-3] We do not recommend prescription of these supplements as their benefit remains unproven, but the risk of their use seems limited to mild stomach upset and the cost of the pills.[1-3] A trial of treatment for 6 months would not be unreasonable if a patient expresses great interest in such products. Future independent high-quality studies are required to further clarify the efficacy of both agents.

Acetaminophen

Acetaminophen is a common first-line analgesic for treatment of hip and knee osteoarthritis. OARSI found the use of acetaminophen to be a core recommendation in 16 of 16 guidelines evaluated.[2] Compared with placebo, statistically significant effects on pain relief have been demonstrated without statistically significant risk of toxicity.[3] OARSI guidelines recommend up to 4 g per day as an effective first-line therapy in patients with mild to moderate pain from OA.[2] Current European League Against Rheumatism (EULAR) recommendations for hip and knee OA suggest that acetaminophen at these doses should be the first choice for mild to moderate pain, and if successful, should be used as the preferred long-term oral analgesic.[2] For most patients the difference in pain relief between acetaminophen and NSAIDs is not clinically significant.[2]

Higher doses of acetaminophen or even prolonged use at recommended doses are not without risk.[2] Although not common in the studies referenced by the guidelines above, acetaminophen overdose can result in hepatoxicity and severe sequelae. Patients should be counseled and monitored regarding their daily dosage. In the absence of an adequate response, or in the presence of severe pain or inflammation (or both), alternative therapy should be considered. Combining acetaminophen with another medication (e.g., ibuprofen) at lower doses of each can also be effective.

NSAIDs

NSAIDs or nonsteroidal anti-inflammatory drugs are among the most commonly used analgesics in the world and are often used as first-line medications for joint pain. One UK telephone survey in 2003 reported that 50% of respondents with osteoarthritis were taking NSAIDs.[2]

There is good level I evidence for the analgesic effect of NSAIDs in OA, and meta-analyses of short-term, placebo-controlled randomized trials have shown an effect size between 0.23 and 0.32 in terms of reduction in pain.[2]

NSAIDs, however, are associated with more adverse effects than acetaminophen.[2,3] Gastrointestinal (GI) discomfort occurs more frequently and, more importantly, serious complications such as peptic ulcers, perforations, and bleeds are more likely to occur.[2,3] Pooled relative risk compared to placebo is estimated at 270%.[2] Risk also increases with age, concurrent use of other medications, and duration of therapy.

In patients at greater GI risk, there is level I evidence that NSAIDs should be used in combination with a proton pump inhibitor or misoprostol for gastroprotection, or that the use of a COX-2 selective agent should be considered.[2,3] Gastroprotection is recommended in all eight of the guidelines where NSAIDs are considered for the management of hip or knee OA.[2] COX-2 inhibitors are recommended in all 11 of the guidelines where they are considered.[2] H_2-receptor antagonists do not have similar protective qualities, and the GI benefit associated with COX-2 agents is lost with concurrent low-dose daily acetylsalicylic acid.[2,3]

Cardiovascular (CV) risk is another concern. After rofecoxib was withdrawn from the market due to increased risk of thrombotic events, a number of studies were done to investigate the CV safety of other NSAIDs. Celecoxib and valdecoxib do not appear to have the same risks, and overall CV risk with COX-2 inhibitors has not been found significantly higher than with nonselective NSAIDs.[2] Serious vascular events occur at approximately 1% per year on COX-2 inhibitors versus 0.9% on traditional NSAIDs.[2]

CV risk is greater in patients with a history of ischemic heart disease or stroke, or in patients with risk factors for heart disease such as hypertension, hyperlipidemia, diabetes, smoking, or peripheral arterial disease.[2] Caution should be exercised when prescribing all NSAIDs in these patients.[2]

Renal toxicity is also a concern in selected patients. In patients with congestive heart failure, pre-existing renal insufficiency, or transplanted kidneys, the use of NSAIDs can lead to acute renal failure. Care should be taken to screen for clinical or laboratory evidence of existing diminished creatinine clearance and consideration should be given to follow-up lab analysis after treatment is begun. Renal clearance decreases significantly with age.

In patients with symptomatic hip or knee OA, NSAIDs should be used

at the lowest effective dose and their long-term use should be avoided if possible.[2,3] In patients at greater GI risk, either a COX-2 selective agent or a nonselective NSAID in combination with a gastroprotective agent should be considered.[2,3] All NSAIDs should be used with caution in patients with CV risk factors.[2] Physicians should continue to choose an NSAID on the basis of the agent's overall safety profile and the patient's individual risk factors.

Opioids

Weak opioids have increasingly been used recently for the treatment of refractory pain in patients with hip or knee OA. A number of systematic reviews and meta-analyses of opioids for chronic non-cancer pain, musculoskeletal pain, and OA have provided evidence of efficacy and acceptable safety in short-term trials.[2]

Analysis of 18 randomized placebo-controlled trials of 3244 OA patients showed a moderate effect size for reduction in pain intensity (0.25).[2] However, there was substantial heterogeneity between studies. This was not obviously related to the preparation used or the quality of the RCTs.[2]

A systematic review regarding acetaminophen and codeine combinations indicated a small analgesic benefit over acetaminophen alone (approximately 5%), but adverse effects were more frequent.[2] Another meta-analysis of opioids for chronic non-cancer pain, including OA, demonstrated that only strong opioids were significantly more effective in relieving pain than acetaminophen or NSAIDs.[2]

Benefits associated with the use of opioids, however, are limited by frequent side effects such as nausea (30%), constipation (23%), dizziness (20%), somnolence (18%), and vomiting (13%).[2] One-quarter of patients treated with opioids withdrew from studies. This compared with 7% of placebo-treated patients.[2]

There have been no long-term trials of the use of opioids for OA, and ongoing concerns remain about the risks of dependence. Recovery from arthroplasty surgery is more difficult for patients on chronic opioid therapy, and their optimal outcome may be compromised.[4]

We feel that strong opioid analgesics should be reserved for patients in exceptional circumstances with severe pain who are not candidates for other therapy. Short courses of weak opioids like codeine or tramadol and acetaminophen combinations can be used for brief exacerbations of pain if tolerated.[2] When prescribing these, precautions should be taken: patients should be counseled about their use and potential for dependence. Nonpharmacological therapies should continue and surgical treatments should be considered. It is highly recommended that strong narcotics such as morphine, oxycodone, and hydromorphone not be prescribed for osteoarthritis. Instead, patients should be referred for surgical treatment.

Topical treatments

Topical NSAIDs

Topical NSAIDs can be effective adjunctive treatments or alternatives to oral analgesics in knee OA.[2] A meta-analysis of 13 RCTs, including 1983 patients with hand and knee OA, showed topical NSAIDs to be superior to placebo in terms of analgesia, relief of stiffness, and function, with a reduced relative risk of adverse GI events compared with oral forms.[2] In one large case control study topical NSAIDs were reported to have no more GI side effects than placebo.[2] Topical NSAIDs are less effective than oral NSAIDs in the first week of treatment, but efficacy is apparent within 2 weeks, with pain relief effect sizes of 0.41 and 0.40, respectively, in weeks 1 and 2.[2] Side effects seem limited to local reactions such as burning, itching, and rashes.[2] Placebo effects may be large with topical therapies, and one meta-analysis showed evidence of possible publication bias with underreporting of negative studies.[2] However, topical NSAIDs remain a reasonable option in combination with or as an alternative to other analgesics.

Topical capsaicin

Topical capsaicin creams contain a lipophilic alkaloid extracted from chili peppers that activates and sensitizes peripheral pain and heat receptors by binding and activating specific cation channels.[2] Application to the skin causes a burning sensation initially but can lead to effective analgesia that prevails over the sensation of burning.[2] The efficacy of capsaicin is supported by a meta-analysis of RCTs of its use in the treatment of chronic painful conditions, including a single placebo-controlled trial in 70 patients with knee OA and two RCTs in patients with hand OA.[2] The mean reduction in pain was 33% after 4 weeks of therapy.[2] Treatment is safe, but local burning, stinging, or erythema troubles 40% of patients. The burning sensation also prevents adequate blinding with this agent, which may influence conclusions based on the available data.[2] Despite these shortcomings, topical capsaicin can be a useful alternative or adjunctive treatment in selected patients.[2] A typical dose is 0.025% cream four times a day.[2]

Intra-articular injection

Techniques for injection

Intra-articular injection of the hip generally requires fluoroscopic or ultrasound guidance to ensure accurate placement.

Multiple descriptions exist for intra-articular injection of the knee joint.[5,6] The patient should be supine and relaxed. It is easiest to inject the knee in full extension. All injections should be performed in a sterile manner.[5,6] It's helpful to palpate surface landmarks prior to antiseptic cleansing and draping. A 25-gauge 1 1/2 inch needle should be used. One study found the lateral mid-patellar approach to have the greatest accuracy.[5] More common, and our method of choice, is to use the soft point at the superior lateral pole of the patella between the patella and the femur, with the needle inserted into the suprapatellar pouch at that level. Entry should be deliberate and smooth. Joint effusion can make the process much easier, while factors such as joint degeneration, diminished range of motion, and obesity can make insertion more difficult.[5,6] If the needle meets an obstruction, pull back slightly and adjust the trajectory. Aspiration of joint fluid can be used for confirmation of accurate placement. During injection, patient complaints of increased pain should be considered an indication of possible extra-articular placement.[5,6] The fluid should flow smoothly and cause little or no discomfort. If infiltration is difficult, reposition and reattempt injection as necessary.

Viscosupplementation

Hyaluronic acid (HA) or hyaluronan is a glycosaminoglycan constituent of synovial fluid. Injection of HA preparations into the knee and hip is commonly used to treat osteoarthritis, but there is considerable ongoing controversy about the treatment's efficacy, cost-effectiveness, and benefit-to-risk ratio.[2,3]

Numerous studies have examined the effectiveness of various HA preparations and generally show positive effects, but there are significant concerns in terms of "trial quality, potential publication bias, and unclear clinical significance."[2] Pooled effects from poor-quality trials are as much as twice those obtained from higher-quality ones.[2] In systematic reviews there is significant heterogeneity between studies and evidence to suggest publication bias and overestimation of effect size.[2]

A Cochrane review of 40 placebo-controlled trials with five different hyaluronan products found statistically significant improvements in pain on weight bearing when results were pooled, but improvements were variable.[2] Pain reduction from baseline at 5 to 13 weeks varied from 28% to 54% for pain and 9% to 32% for functional outcome scores.[2] Data to suggest that the higher molecular weight HA preparations were more effective than lower molecular weight preparations were inconclusive.[2] In a randomized comparison of three injections of high and low molecular weight HA, there were significant improvements of approximately 40% in pain and functional scores up to 6 months after treatment.[2] However, in another placebo-controlled trial comparing HA with corticosteroid or saline at 2 weekly intervals, there were no significant differences between the groups.[2]

Discordant conclusions in systematic reviews of HA have been found to be due to inclusion of different controlled trials, differences in the outcome measures and time points selected for extraction, and different statistical methods for data synthesis, which resulted in conflicting estimates of therapeutic effect.[2]

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No major safety issues were detected, but in placebo-controlled trials minor adverse events such as transient pain at the injection site occurred slightly more frequently in patients treated with intra-articular hyaluronan than in those treated with intra-articular corticosteroids.[2]

Because of the conflicting evidence from the literature and existing guidelines, the use of intra-articular HA is not universally recommended.[2,3] Relief may be gained for patients with mild to moderate hip or knee OA symptoms, and results are characterized by delayed onset but prolonged duration.[2] The adequacy of clinical benefit remains somewhat unclear and costs are not insignificant—injections typically range from $130 to $230 per injection and 3 to 5 weekly injections are required. We tend not to recommend these injections, particularly in patients with moderate to severe disease, but if patients are given realistic

expectations and have adequate resources, a trial of therapy is not unreasonable, particularly for mild OA.

Corticosteroid therapy

Despite the unclear role of inflammation in the pathogenesis and progression of osteoarthritis, 11 of 13 existing treatment guidelines recommend injection of corticosteroids for OA at some stage of the disease.[2] Multiple systematic reviews conclude that it is effective for relieving pain at least in the short term (i.e., 1 to 2 weeks).[2,3,7] The efficacy is also supported by evidence from a Cochrane systematic review, which examined data from 13 randomized placebo-controlled trials.[2,8] The effect size for pain relief is in the moderate range (0.25) at 2 and 3 weeks after injection, with a lack of evidence for pain relief by 4 weeks and 24 weeks after injection.[2,8] Evidence for hip steroid injection is more limited, and mixed in terms of results.[2]

Some randomized controlled trials have demonstrated better outcomes in patients with synovial effusions or other clinical signs of inflammation, but this has not been seen universally and it remains controversial whether steroid injections should be restricted to these patients.[2] The analgesic effect may be due to additional mechanisms unrelated to the purely anti-inflammatory effect.

In terms of toxicity, potential side effects include post-injection flares of pain, crystal synovitis, hemarthrosis, joint sepsis, articular cartilage atrophy, and steroid-induced arthropathy. Side effects such as bruising and lipodystrophy are not uncommon but can be minimized with careful technique. Overall, in 28 controlled trials of intra-articular steroid injections in 1973 patients with OA of the knee, no serious adverse events were reported as a consequence.[2] In cases where inflammatory or infectious arthritis is considered, aspiration and analysis of synovial fluid prior to injection should also be considered.

OARSI guidelines state that intra-articular injections with corticosteroid can provide short-term symptomatic relief of knee OA, and should be considered, particularly in cases of moderate to severe pain not responding to other analgesics and nonpharmacologic modalities.[2] Anecdotally we have found a small percentage of patients to achieve long-term improvement. For the most part, however, improvements are short-lived for what is a chronic problem.[7] Too few head-to-head comparisons exist to support any particular choice of corticosteroid, and data are insufficient to state how frequently it is safe to repeat injections. More than four times annually is generally not recommended. One indication for these injections is if a patient needs to be active for a short period of time while awaiting surgery, either because of work or family commitments. The temporary relief, particularly if the patient is clearly informed about its temporary nature, is often appreciated.

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Antidepressants

Depression and osteoarthritis are both common and often coexist. Multiple studies have demonstrated that psychosocial factors are equally or more important than disease-specific factors in reports of pain intensity and disability in several conditions, including joint pain.[9,10] Awareness and treatment of depressive symptoms can result in significantly less pain and improved quality of life.[9,10] In one study of older adults with arthritis and comorbid depression, treatment of depression extended beyond improved mood to significant improvement in pain, function, and quality of life.[10]

When to refer

The decision to refer a patient for surgery is complex, and consensus statements fail to agree upon specific thresholds for referral, but pain and disability are consistently the most important measures considered.[11-13] Physical examination is emphasized less and tends not to correlate with the decision for surgery.[12,13] The ability to work, give care to dependants, and live independently consistently outweigh range of motion or other measures of physical impairment.[13]

Generally, referral to an orthopaedic surgeon should be made when intrusive pain or disability persists despite

a substantial trial of nonsurgical therapy, or when long-term opioids, high-dose acetaminophen or NSAIDs, and repeated intra-articular injections are required to control symptoms. The decision should be personalized and based on each patient's experience of the disease, functional goals, and risks of undergoing elective surgery.

Age, obesity, and comorbidities have little impact on the benefit from joint replacement and rarely should prevent referral.[14] Hip and knee replacement surgeries reliably reduce pain, restore function, and have low morbidity and mortality.[15,16] With improving joint arthroplasty survivorship, it has also become a viable option for younger patients with disabling disease. Decision making in these cases can be challenging, and orthopaedic consultation may be the best way to determine suitability for surgery. It is important to note that there is no age restriction for joint replacement surgery, and referral should not be withheld because of young age.

Conclusions

Pharmacological treatments for osteoarthritis of the hip and knee have not been shown to alter the progression of disease but may be used in a multitude of combinations for symptom relief. A range of oral analgesics, topical treatments, and intra-articular injections of hyaluronic acid or steroids might be considered. Treatment should be individualized according to patient symptoms, preferences, and a therapeutic agent's overall safety profile. When intrusive pain or disability persists despite a substantial trial of nonsurgical therapy, or when controlling symptoms requires long-term opioids, high-dose acetaminophen or NSAIDs, and repeated intra-articular injections, referral for surgical options should be considered.

Competing interests

None declared.

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