Published in final edited form as:
Pain Med. 2012 June ; 13(6): 740–753. doi:10.1111/j.1526-4637.2012.01394.x.

Evidence based knee injections for the management of arthritis

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Abstract

Objective—Arthritis of the knee affects 46 million Americans. We aimed to determine the level of evidence of intraarticular knee injections in the management of arthritic knee pain.

Methods—We systematically searched PUBMED/MEDLINE and the Cochrane databases for articles published on knee injections and evaluated their level of evidence and recommendations according to established criteria.

Results—The evidence supports the use of intraarticular corticosteroid injections for rheumatoid arthritis (1A+ level), osteoarthritis (1A+ level), and juvenile idiopathic arthritis (2C+ level). Pain relief and functional improvement are significant for months up to one year after the injection. Triamcinolone hexacetonide offers an advantage over triamcinolone acetonide and should be the intraarticular steroid of choice (2B+ level). Intraarticular injection of hyaluronate may provide longer pain relief than steroid injection in osteoarthritis (2B+ level). It can also be effective for rheumatoid arthritis knee pain (1A+ level). However, it is only recommended for patients with significant surgical risk factors and for patients with mild radiographic disease in whom conservative treatment has failed (2B± level). Botulinum toxin Type A injection is effective in reducing arthritic knee pain (2B+ level) and so is tropisetron (2B+ level) and tanezumab (2B+ level). The new agents, such as rAAV2-TNFR:Fc, SB-210396/CE 9.1, and various radioisotopes have provided various degrees of success, but their long-term safety and efficacy remains to be determined.

Conclusions—We conclude that strong evidence supports the use of intraarticular knee injection as a valuable intervention in the continuum of management of arthritis between conservative treatment and knee surgeries.

Keywords

Knee injection; Rheumatoid arthritis (RA); Osteoarthritic (OA); Juvenile rheumatoid arthritis (JRA); Intraarticular corticosteroid injection (IACI); Hyaluronic acid (HA); Radiation synovectomy (RSO)

Introduction

The knee is one of the most commonly affected joints of arthritis which affects an estimated 46 million (22%) of adults in the US (1,2). Radiographic evidence of knee osteoarthritis (OA) increases with age, from 27% in subjects younger than age 70 to 44% in subjects age 80 or older (3). Nearly half of all adults will develop symptomatic knee OA by the age of 85, with lifetime risk highest among obese persons (4). Rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA), (also called juvenile idiopathic arthritis (JIR), juvenile

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chronic polyarthritis, and Still's disease) are also common and affect millions of children and adults in the US (1, 2, 5). As a result, knee injections are routinely performed by physicians of various specialties. The first report on a series of 9 knee injections of iodoform and glycerin was dated back to 1897. This intervention allowed for the avoidance of knee amputation and provided functional recovery (6). Over the next 60 years, there were only a few articles published regarding knee injections. Since the 1960s, knee injections of steroids, and various other agents, have become widely available for the symptomatic management of pain and movement limitations associated with arthritis. There have been thousands of papers published over the last 50 years in regards to knee injections. While the available systematic reviews with meta-analysis provide quantitative evidence, they are narrowed to certain agents or specific conditions (7). Therefore, they are inherently missing the broader view on this topic. In addition, they become outdated quickly because of a large amount of newer clinical trials. This review focuses on the recent advancement of intraarticular knee injections based primarily on evidence provided by systematic reviews with meta-analysis and clinical trials when the systematic assessment of quantitative evidence is not available. A narrative overview of important practical points included in this article highlights the important details that may be of particular interest to practicing physicians. We have recently reviewed complications associated with joint injections elsewhere (8).

Methods

We systematically searched PUBMED/MEDLINE and the Cochrane databases for all reports published in any language on knee injections. The search in PUBMED/MEDLINE and Cochrane databases was performed using the following key words: knee, injection, injections, when looking for all related publications between the earliest available date (the first knee injection in the PUBMED/MEDLINE dated 1897) and December (week 3) of 2010. There were no language restrictions. The following is an example of the query that was performed for the PUBMED/MEDLINE database: ("knee"[MeSH Terms] OR "knee" [All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields]) AND (("injections"[MeSH Terms] OR "injections" [All Fields] OR "injection"[All Fields]) OR ("injections"[MeSH Terms] OR "injections" [All Fields])). Records from the query were further filtered to extract evidence-based publications in the format of systematic reviews, which included systematic reviews, meta-analyses, and clinical trials. A further manual search was undertaken to exclude non-relevant papers by the title. The abstracts were subsequently reviewed and the full text publications were retrieved whenever necessary. Only those publications of systematic reviews, meta-analysis, and clinical trials/observational study of historical interest were chosen for this review. The level of evidence and implications for recommendations of the all-included studies were graded according to Guyatt and co-authors, modified by our groups (9,10) (Table 1). This method of level of evidence classification takes into account of the type of the study (systematic review with/without meta-analysis, randomized controlled trials (RCT), or observational study), the quality of the study (methodological design such as sample size and power analysis), and the quantity of studies included in meta-analysis and systematic reviews. The level of evidence of systematic reviews or meta-analyses was graded according to the same scale, by the quality of studies incorporated into a particular meta-analysis or systematic review. Two of the authors (O.C. and D.S.) independently performed the search and extracted data from articles. The extraction of publications thought to be of interest for pain physicians was also performed (B.V. and J.C.). Any disagreements were resolved by discussion.

Results and discussion

The query yielded 4304 records. There were 46 systematic reviews, including 31 with meta-analysis, and 871 clinical trials, including 642 randomized controlled trials records identified. The Cochrane database search identified 86 systematic review records and 817 clinical trials. The publications reviewed in this article resulted from subsequent manual search to exclude non-relevant papers based on the title and/or the content of the abstracts. The literature had a common focus on the comparative effectiveness of the various injectates of knee injections. We did not find publications that focused on comparing different technical approaches (such as knee position and needle site, blind injection versus ultrasound or fluoroscopy guided injection). Nevertheless, it is true that most of the injections were performed at an injection site above the tibial plateau and lateral to the patellar tendon with the knee flexed at about 90 degrees and without ultrasound or fluoroscopy guidance. We thus organized the review by material injected. We also tabulated the key findings by the types of arthritis to facilitate cross reference and improve clarity (Tables 2 and 3).

Steroid injection

Intraarticular corticosteroid injection (IACI) of the knee is a well-established procedure. Evidence of effectiveness of IACI in RA was reported in a meta-analysis (11) (1A+ level). Five RCTs (n=346) which addressed the effectiveness of IACI over the placebo were identified. There was evidence that the injections improve pain, knee flexion and extension, knee circumference, morning stiffness, and duration of efficacy (up to 22 weeks in the steroid-treated groups compared to 1 week in the placebo treated groups). The effectiveness of IACI may be dose-related. There was no evidence of harm so it is appropriate that IACI continues to be used and be properly evaluated.

Two meta-analyses evaluated the effect of IACI on OA of the knee. Five RCTs (n=312) showed clinically and statistically significant reduction of osteoarthritic knee pain 1 week after injection. The beneficial effect could last for 3 to 4 weeks, but is unlikely to continue beyond that (12) (1A+ level). The second meta-analysis showed that the numbers needed to treat to get one improvement was 1.3 to 3.5 patients (13) (1A+ level). The improvement of symptoms after IACI only lasted up to two weeks. A dose equivalent to 50 mg of prednisone may be needed to show longer benefit.

The main beneficial effect of IACI is pain relief (14). The duration of this effect is variable. Inflammatory problems generally had a higher rate of favorable response in terms of pain and function. IACI at the knee joint in JRA resulted in remission for >6 months in >80% of the patients with a mean duration of approximately 1.2 years. Pain relief was 8 weeks in RA and only 4 weeks in OA. IACI may also induce remission in patients with oligo-/polyarthritis and in patients with extra-articular manifestations. In addition to pain relief, IACI also improved gait patterns in terms of walking velocity and joint moments in patients with juvenile rheumatoid arthritis (JRA) (15) (2C+ level). It is noteworthy that IACI influences the gait pattern also in joints that have not been injected. Clinical trials also suggest that early and continued use of IACI may be associated with less leg length discrepancy in young children with pauciarticular JRA (16) (2C+ Level). This may indicate decreased duration of synovitis. In addition to clinical and kinematic observations, quantitative magnetic resonance imaging (MRI) can differentiate between therapeutically induced changes in inflammation and synovial proliferation in RA of the knee and is sensitive enough to detect change after one week (17) (2C+ level).

Comparison between injections of triamcinolone hexacetonide (TH, Aristospan) and triamcinolone acetonide (TA, Kenalog) in treatment of JRA suggest that TH offers an

advantage to TA and should be the intraarticular steroid of choice (18) (2C+ level). The mean time to relapse was over 10 months in the TH group (114 joints) and less than 8 months in the TA group (113 joints). Triamcinolone was compared to betamethasone and methylprednisolone in a 2009 systematic review of studies on patients with OA. It appeared that triamcinolone was more effective than betamethasone and methylprednisolone, though not all of the studies used a validated outcome measure such as the VAS pain scale (19) (1B + Level). Also, remission in patients with JRA was longer with concomitant treatment with TH, methotrexate, and general anesthesia for the procedure (20) (2C+ Level). Furthermore, aspiration of synovial fluid can reduce the risk for arthritis relapse when treating RA patients and arthrocentesis should thus be included in the IACI procedure (21) (1B+ Level). Moreover, there is some evidence to support the use of IACI and resting a knee following injections (11) (2B± level). The studies involved adult participants so any conclusions can only be applied cautiously to children. Further research is required to examine the use and type of rest and the differential responses of different joints following injections. A significant proportion of rheumatologists and general practitioners performing steroid injections of the knee advise patients not to weight-bear post-injection for one or two days (22) (0 Level).

Comparisons between the 3 most common treatment strategies for knee monarthritis: nonsteroidal antiinflammatory drugs (NSAIDs) only, NSAID trial followed by IACI if arthritis was not resolved after 2 months, and initial IACI, suggest that initial IACI appears to be the optimal treatment strategy for knee monoarthritis in JIA (23) (2C+ Level). The NSAID trial strategy may avert IACIs in some patients, but at a cost of continued active arthritis. The number of patients that need to be treated with the NSAID trial strategy to avoid a single IACI compared with the initial IACI strategy is 3.8 with an expected additional cost of 6.7 months of active arthritis. The large majority of patients (92%) preferred the initial IACI strategy.

Repeated intraarticular injections of 10 mg methotrexate were compared with a single injection 40 mg triamcinolone hexacetonide in patients with definite RA and knee effusions (24) (2C+ level). The intraarticular granulocyte counts and IL-8 levels decreased in all methotrexate treated patients on day 10–13 and stayed low in those patients who could be re-evaluated after 13 weeks. Compared to the IL-8 levels, the other tested cytokine levels showed only minor changes on day 10–13. Intraarticular methotrexate therapy results in a strong decrease of SF-granulocyte counts. This effect may be due to the impairment of IL-8 mediated chemotaxis by decreased IL-8 synthesis in synovial fluid mononuclear cells. Clinically, repeated intraarticular methotrexate therapy resulted in a worse 13 week outcome than IACI treatment measured in an intention-to-treat analysis.

Addition of 600 mg rifampicin or 50 mg methotrexate to the injection of 20 mg triamcinolone hexacetonide was tested in RA (25) (2B+ level). Eighty-two patients on stable therapy were allocated at random to receive intraarticular TH alone, TH and methotrexate (TH+M) or TH and rifampicin (TH+R). Pain was significantly better in the TH+R group compared with TH alone (P=0.039, Mann Whitney U). The median duration of improved pain scores was 13.5 weeks with TH alone, 10 with TH+M and 19 with TH+R. Examination and microwave thermography revealed improvements compared with baseline, but there were no significant differences between the groups. Eleven of 28 patients treated with TH+R developed a flare of post-injection pain. It is concluded that while the addition of rifampicin improved pain relief, post-injection pain associated with rifampicin needs to be addressed.

There are systemic effects associated with IACI (26). Serum cortisol decreased within hours with a nadir after usually 24–48 h following the IACI. Recovery to baseline takes 1–4 weeks and sometimes longer depending on the type and dose of IACI and on the number of

injected joints. Serum cortisol levels were blunted following adrenocorticotropic hormone stimulation in a small proportion of patients following methylprednisolone acetate injection and more common following other preparations. IACI resulted in a transient increase in blood glucose levels over few days in controlled diabetic patients with peak levels around 300 mg/dL. IACIs are associated with reduction in inflammatory markers like C-reactive protein and erythrocyte sedimentation rate that started a few days following the IACI and could last for months. The effect on inflammatory cytokines is immediate with a significant decrease within hours. The release of corticosteroid into the circulation also provides some generalized improvement. This can prove helpful during the management of flares of inflammatory disease. These systemic effects of IACI may be related to remission of extra-articular manifestations.

Adverse effects are either rare or insignificant (8,14). There was no joint space loss at the knee joint following multiple IACI in OA and also no increase in cartilage or bone erosions in RA following a single IACI. Abnormal uterine bleeding, hypertension, and hyperglycemia rarely cause problems (27). The risks are mainly related to the discomfort of the procedure, localized pain post-injection, and flushing. Application of 2.5g lidocaine/prilocaine cream for 60–90 min had no statistically significant analgesic effect on pain associated with injections of steroids into the knees of children with juvenile arthritis (28) (2B− Level). Septic arthritis rate is very low and probably occurs in about 1 in 10,000 injections. Careful aseptic technique is the best protection. Other rare adverse effects included intraarticular and periarticular calcifications, cutaneous atrophy (~2%), cutaneous depigmentation, avascular necrosis, rapid destruction of the femoral head, acute synovitis, Charcot's arthropathy, tendinopathy, Nicolau's syndrome, and joint dislocation.

Hyaluronate injection

Intraarticular injections of hyaluronic acid (HA) have been advocated for treatment of symptomatic knee in OA. HA is the major constituent of a 1-2-micron layer on the surface of articular cartilage as well as a major constituent of synovial fluid (SF). Solutions of HA can act as lubricants when movements are slow and as shock absorbers when movements are fast. HA may thus protect the articular cartilage and soft tissue surfaces from trauma during joint function. In arthritis, the molecular weight of HA is reduced, and so are its protective properties. Intraarticular HA may provide a way of reversing this and may also have anti-inflammatory effect. HA is thus used to relieve pain and improve function, usually in patients with knee OA. Hyaluronan preparations available in the US include sodium hyaluronate (Hyalgan, Supartz, or Euflexxa), Hylan G-F 20 (Synvisc), and high-molecular-weight-Hyaluronan (Orthovisc) (29).

There were 7 meta-analyses of the effectiveness of IA injection of HA for the treatment of knee osteoarthritis compared to placebo or IACI, five of which found IA injection of HA efficacious in the management of OA (30–34) (2B+ levels) while the other two did not show significant effects (35,36) (2B− level). Nine out of 10 guidelines on management of knee OA contained positive recommendations on the use of HA (37).

A early study reports that approximately 2/3 of treated knees received 2/3 relief of pain in 80 knees with symptomatic OA treated with HA (38) (2C+ Level). HA treatment is not appropriate for all patients with knee OA. Overall, less than 50% of treated knees achieved satisfactory results, and only 35% reported increased activity. Twenty-two patients (28% of knees) underwent surgery within 7 months of their injection, suggesting an inadequate response to treatment. The treatment is not without complication because 11 patients (15% of knees) experienced adverse reactions, including one case of septic arthritis. The authors recommend intraarticular HA only for patients with symptoms and significant surgical risk factors and for patients with mild radiographic disease in whom conservative treatment has

failed (physical therapy, weight loss, NSAIDs, and IACI). It is inadvisable to treat patients with a complete collapse of joint space or bone loss with intraarticular HA, given their poor clinical response.

Intraarticular injection of HA may by effective for up to 3 months for OA knees, significantly better than the placebo (39) (2B+ level). The effective peak was one week after weekly injections for five consecutive weeks. The effective period could last up to three months without additional treatment. The efficacy on OA knees was more prominent for relief of motion pain and improvement of knee movement. No side effects developed during a six month period in this study.

More recent studies showed seemingly conflicting results in patients receiving intraarticular HA injections for OA (35) (2B− level). While some studies showed clinically meaningful positive effect, the more recent FLEXX trial, however, suggests that the positive effect may be questionable (40) (2B± level). In this prospective study of 588 subjects at 26 weeks there was a 53% reduction of pain from baseline in patients who received three weekly intraarticular injections of bioengineered 1% sodium hyaluronate (EUFLEXXA) as compared to a 38% reduction in patients who received intraarticular saline. Of note is the seemingly high 38% reduction in pain in the patients who received saline injection. In a study of 337 patients evaluated over 1 year, however, it was found that intraarticular sodium hyaluronate (Hyalgan) injected weekly for 5 weeks had no significant difference from saline (41) (2B− level). These results are seemingly conflicting but may be explained by differences in the experimental designs and the duration of the observations.

Intraarticular injection of polynucleotide gel was compared to hyaluronan in 60 patients with OA and both groups achieved statistically significant pain reduction, though no significant difference between the two groups (42) (2B+ level). Condrotide-Turnover Joint is a new product composed of polynucleotides 20 mg/ml which bind water and form a 3-D gel that can moisturize articular surfaces. Polynucleotides are natural derivatives of fish sperm that are sterile and apyrogenic but with viscoelastic and trophic properties. This may represent a new direction of research.

Comparisons between placebo, glucocorticoids and viscosupplementation in patients with OA suggest that HA had a slightly longer period of benefit than triamcinolone hexacetonide or placebo (43) (2C+ level). Current evidence suggests that viscosupplements probably provide a similar level of pain relief to glucocorticoids and do so for several months, but the onset is slower, and there is a potential for local adverse reactions. There is a large placebo effect from intraarticular injections, and the benefits of intraarticular glucocorticoids may be only slightly better than this effect in the OA population. Studies of intraarticular HA also show a marked placebo response, which may be more prolonged than that of glucocorticoids. Sodium hyaluronate and corticosteroid appear to have comparable clinical effects, but affect differentially on specific biomarkers (44) (2B+ level). Sodium hyaluronate may have protective effects on articular cartilage by increasing the hyaluronase concentration in synovial fluid. There may also be inhibitory effects on the catabolism of articular cartilage by reducing the concentration of matrix metalloproteinase (MMP-9). Other marker levels did not differ significantly between groups.

One meta-analysis assessed the efficacy of IA injections of HA in patients with RA (45) (1A + level). Data from 5 RCTs (720 RA patients) was pooled for meta-analysis and the results indicated that IA HA is an effective and safe alternative therapy for the RA knee as it provided reliable pain reduction and reduction in inflammation. No serious side-effects were reported, while minor adverse effects were only reported in patients after HA treatment. Arthrocentesis is effective in reducing the risk for arthritis relapse after IA injection of HA

to rheumatoid knees with joint effusion, as suggested in a study of 118 patients (46) (2B+ level). Predicting responders are duration of knee arthritis, C-reactive protein, and radiological scores.

Induction of acute calcium pyrophosphate dihydrate arthritis after the intraarticular injection of Hylan G-F 20 (Synvisc) has been reported in three cases (47) (0 level). Pain and swelling of the knee occurred a few days after injection of Hylan G-F 20, accompanied by a severe loss of physical function. A microscopic investigation of the synovial fluid showed evidence of calcium pyrophosphate dihydrate crystals. Bacterial contamination was not detected. Some days after receiving NSAIDs and an intraarticular injection of steroids, the symptoms disappeared.

Injection of radioisotopes

Radiation synovectomy (RSO) is a useful treatment modality in RA patients with refractory knee synovitis. Forty-nine studies were included in a meta-analysis on 90Yttrium-RSO used predominantly in knee joints (48). The reported success for 90Yttrium was 24–100% at 6–12 month (1A+ level). At 6 months, the pooled odds ratio favoring RSO of the knee with Yttrium over control (GC or saline injection) was 4 (confidence interval 95% 1.2–14, p=0.02), but was not significant at 12 months.

In the first study of radiation synovectomy using 188Re-tin-colloid for patients with rheumatoid arthritis, the treatment resulted in an improvement of arthritis and was well tolerated (49) (2C+ level). Radiation synovectomy using 188Re-tin-colloid was performed in 22 knees from 21 RA patients refractory to intraarticular corticosteroid injection. Pain intensity on a visual analogue scale decreased significantly 12 months after therapy (68 mm vs. 25 mm). Pain decreased in 19 cases (86.3%), joint tenderness improved in 14 cases (63.6%) and joint swelling was reduced in all cases (100%). 188Re-tin-colloid was safe with residual activity of 0.077% of the injected dose in the blood and 0.14% in the urine. No clinical side-effects or abnormalities in leucocyte count, platelet count, liver function tests or urine analysis were observed in any patient. Radiation synovectomy using Re-tin colloid in refractory RA patients improved magnetic resonance imaging (MRI) findings as well as clinical parameters (50) (2C+ level). Sixteen patients with RA refractory to intraarticular corticosteroid therapy were treated with intraarticular injection of Re-tin colloid. Synovial thickening measured by gadolinium-enhanced MRI of treated knees improved in 87.5% of patients at 6 months after therapy. Pain intensities on a visual analogue scale were significantly lower, joint swelling improved, range of motion increased, and joint tenderness decreased in treated knees after 6 months. The contralateral control knees did not show any significant clinical improvement.

One of the concerns over radionuclide synovectomy is radiation doses delivered to non-target organ systems due to leakage of radioactive material from the articular cavity. Comparisons have been made between extra-articular leakage values of the 3 commonly used radiopharmaceuticals; 90Y-citrate, 90Y-silicate and 186Re-sulfide colloid in 35 patients with persistent synovitis (51) (2C+ level). No visible leakage was observed. The median leakage values calculated for 90Y-citrate, 90Y-silicate and 186Re-sulfide were found as 1.9%, 2.4% and 2.7%, respectively. There was no significant difference in terms of extra-articular leakage between the 3 radiocolloids.

Radiation synovectomy is frequently combined with intraarticular corticosteroid injection in the treatment of RA to reduce local inflammation and lymphatic clearance of radiocolloid. Whether simultaneous corticosteroid injection together with radiocolloids is necessary in other forms of chronic synovitis is investigated in patients with hemophilia (52) (2C− level). One of 12 patients who had knee arthroplasty was previously found to have a high amount

of leakage, 70% of radiocolloid at the injection site drained into the pelvic lymph nodes. In the remaining 11 patients, no lymph nodes were visualized in the groin area and the measured average leakage for these patients was 2.3%. It is suggested that in cases of appropriate particle size and strict immobilization of knee joints (splinted for 48 hours), leakage of radiocolloid was minimal and steroid coinjection might not be necessary for radiosynoviorthesis of patients with hemophilia with chronic knee synovitis.

Samarium-153 particulate hydroxyapatite has also been evaluated in patients with persistent rheumatoid knee synovitis (53) (2C+ level). Intraarticular injection of samarium-153 particulate hydroxyapatite combined with triamcinolone hexacetonide was performed in 18 patients who had failed to obtain more than 4 weeks symptom relief from a prior intraarticular glucocorticoid injection. Symptom relief was maintained in 56% patients at 6 months and in 44% of patients at 12 months following treatment. Median duration of symptom relief was 9 months. No unwanted effects from the treatment were observed. However, a later double blind controlled trial did not show clear beneficial clinical effect of combined Sm-153 PHYP/triamcinolone hexacetonide injection over triamcinolone hexacetonide alone a year after treatment for chronic knee synovitis (54) (2B− level).

Injection of other agents

Intraarticular injections of botulinum toxin Type A (BoNT/A) for refractory joint pain were reported in a case series review of 12 month clinical experience (55) (2C+ level). Eleven patients (15 joints) with chronic arthritis who were not surgical candidates were injected. All patients were on analgesic and/or anti-inflammatory medications and all joints had previous intraarticular steroid or viscosupplement injections with inadequate or unsatisfactory benefit. A clinically and statistically significant improvement was noted after IA-BoNT/A injections. The mean maximum decrease in lower extremity joint pain was 55% and 36% at 4 and 10 weeks after injection respectively. This report was confirmed by a recent RCT, which demonstrated that intraarticular injection of BoNT/A is an effective and safe treatment for chronic joint pain disorders (56,57) (2B+ level). Mechanistically, BoNT/A may interact with the nociceptive neurons, as we have recently shown (58), and/or act centrally through retrograde axonal transport (59–61) to produce analgesic effects that are independent of muscle relaxation. Animal experiments demonstrate that BoNT/A inhibits not only the exocytosis of acetylcholine at the neuromuscular junctions but also other neurotransmitters such as glutamate, substance P, and calcitonin gene related peptide (62–64), all of which have been indicated in pain transmission (65–71).

Intraarticular morphine was tested in chronic arthritis in a randomized double-blind study (72) (2B+ level). Comparison was made between intraarticular morphine (3 mg), dexamethasone (4 mg) and saline (3 ml) in 44 patients with chronic inflammatory arthritis or OA of the knee. During the first 6 h after injection both morphine and dexamethasone significantly reduced VAS and pain rating indices (PRI) in comparison to saline. Both substances also produced a significant reduction of PRI compared to saline during the subsequent 5 days. No patient displayed untoward side effects. Synovial leukocyte counts were lower after morphine than after saline. It is concluded that, intraarticular morphine produces analgesia of similar magnitude to dexamethasone and it may have antiinflammatory actions in chronic arthritis.

The pain in arthritic knees has been associated with increased expression of nerve growth factor. The hypothesis of analgesic efficacy of tanezumab, a humanized monoclonal antibody that binds and inhibits nerve growth factor, was recently studied in 450 OA patients (73) (2B+ level). The mean reductions from baseline in knee pain while walking ranged from 45 to 62% with various doses of tanezumab, as compared to 22% with placebo. The rate of overall positive clinical response ranged from 74 to 93% with tanezumab

treatment, compared to 44% with placebo. The rates of adverse events were 68% and 55% in the tanezumab and placebo groups, respectively.

Interestingly, this concept was tested in 91 patients with OA, when the platelet-rich plasma (PRP), a natural concentrate of autologous growth factors from the blood, was injected IA in 115 knees (74) (2C+ level). The hypothesis was that the utilization of PRP could bring a stimulation of the chondral anabolism and a reduction of the catabolic processes. The procedure consisted of 150-ml of venous blood collected and twice centrifugated: 3 PRP units of 5 ml each were used for the injections. Clinical evaluation before and at the end of the treatment, and at 6 and 12 months follow-up showed that younger patients responded for the treatment, with improved activity in daily living up to 6 months after the injection. Improvement in only 30% of the patients older than 65 years was noted.

Intraarticular injection the 5-HT3 receptor antagonist tropisetron was equally effective compared with methylprednisolone in a double-blind study (75) (2B+ level). Thirty-four patients with gonarthritides or activated OA (18 patients with rheumatoid arthritis, 16 patients with OA) were treated with a single intraarticular injection of 10 mg tropisetron (18 patients) or 40 mg methylprednisolone (16 patients). The results showed that by means of the intraarticular tropisetron treatment, the inflammatory joint process with arthritides and activated arthroses could be influenced in a similar way as with corticosteroid treatment. No significant differences were detected. It appears that intraarticular treatment with the 5-HT3 receptor antagonist tropisetron in patients with gonarthritides and activated arthroses was about equally effective as those for treatment with corticosteroids. It may be used as an alternative in patients for whom concomitant diseases like diabetes and hypertension make it difficult to use corticosteroids. Whether increasing the tropisetron dose may further improve the results remains to be determined.

Intraarticular injection of SB-210396/CE 9.1, an anti-CD4 monoclonal antibody that has documented efficacy in RA when given intravenously, appears to be safe and efficacious (76) (2B+ level). Thirteen RA patients with active, resistant knee synovitis, were randomized to intraarticular injection of placebo (n=3), 0.4 mg (n=3) or 40 mg (n=7) of anti-CD4 after sequential dynamic gadolinium enhanced MRI, followed by same day arthroscopy and synovial membrane biopsy. Imaging and arthroscopic synovial membrane sampling were repeated at 6 weeks. Twelve patients completed the study (one placebo treated patient refused further MRI). Arthroscopic improvement was observed in 0 of 2 placebo patients but in 10 of 10 patients receiving active drug (>20% in 6 of 10). Improvement in MRI was consistently observed in all patients of the 40 mg group but not in the other two groups. A reduction in SM CD4+ score was noted in the 40 mg group and in the 0.4 mg group. Strong correlations both before and after treatment were identified between the three imaging modalities. Intraarticular delivery of SB-210396/CE 9.1 appears to be well tolerated, safe, and efficacious in improvement of coordinated MRI, arthroscopic, and histological imaging.

Intraarticular injection of 1g immunoglobulin G (IgG) was used to assess local anti-inflammatory effects of high dose IgG in RA (77) (2B− level). Eleven patients with RA, having flare-up of knee joint synovitis, were included in the study. Six received an intraarticular injection of 1g of IgG in 10 ml saline and five received an intraarticular injection of 10 ml physiological saline alone. The effect of the treatment was evaluated clinically and by magnetic resonance imaging using gadolinium contrast enhancement. In one of the six patients that received intraarticular IgG and one of the five control patients a modest decrease of synovial hypertrophy was noted. None of the patients experienced clinical improvement as a consequence of the treatment. The results of this study do not support local administration of IgG as an anti-inflammatory treatment in patients with RA.

Intraarticular injection of rAAV2-TNFR:Fc, an adenoassociated virus serotype 2 vector containing the cDNA for the human tumor necrosis factor (TNF)-immunoglobulin Fc fusion gene (tgAAC94) has been tested in a phase 1 study in 15 subjects with inflammatory arthritis (78) (2B+ level). Intraarticular injection of rAAV2-TNFR:Fc was well tolerated with no major safety issues. At 12 weeks after injection, a two-point decrease in swelling was noted in 2/11 and 2/4 subjects injected with rAAV2-TNFR:Fc and placebo, respectively. Synovial fluid TNFR:Fc protein was not detected (nor expected) at the doses used. A single dose of intraarticular rAAV2-TNFR:Fc appears to be safe and well tolerated in subjects without concurrent systemic TNFα antagonist use. It is thus feasible to proceed with larger trials to further test the safety and efficacy of local TNFR:Fc gene transfer as a therapeutic modality for patients with inflammatory arthritis.

An IA administration of anakinra, a recombinant form of competitive antagonist of human IL-1 receptor, initially was found to be beneficial in a small observational study of 13 patients with OA (79) (2C+ level). However, recent RCTs results produced conflicting results (80,81) (2B+, 2B− levels).

There have been studies evaluating the effect of various subcutaneous, rather than intraarticular, injections for the treatment of knee OA. Subcutaneous injection of Articulatio Genus D5 (AG5), a cartilage preparation, was injected subcutaneously three times a week for 4 weeks in the affected knee in a study of 91 OA patients (82) (2B+level). This was not superior to placebo in terms of arthritis index scores, but was found to reduce pain and have an opioid-sparing effect that could prompt further research. In a small study of 20 patients, the injection of sodium pentosan polysulfate (Pentosan) led to improvements in functional outcome and patient satisfaction (83) (2C+ level). Pentosan is a semi-synthetic drug manufactured from hemicellulose with an average molecular weight of 5700 Daltons. It was designed to work as a heparin-like agent that interferes with binding of factor Xa to thrombin by an AT-III-independent mechanism. It has been used as thrombosis prophylaxis and treatment of phlebitis for 50 years in Europe, but not considered previously for arthritis. It is intended to reduce cartilage degradation by decreasing inflammatory mediators such as MMP-3, IL-1 and TNFα. It increases the amount of proteoglycan incorporated into extracellular matrix and increases the synthesis and molecular weight of hyaluronan.

Many other agents have been injected intraarticularlly or periarticularly in the treatment of knee pain. These include silicone (84), lactic acid(85), osmic acid (86), orotein(87), dextrose prolotherapy (88), non-steroidal anti-inflammatory drugs (89), glucosamine (90), somatostatin(91), chloroquine (92), mucopolysaccharide polysulfuric acid ester (93), cytostatica (combination of osmic acid, and alkylating agents thio-tepa and azetepa) (94), herbal alkaloid ligustrazine (95), and saline lavage (96,97). However, these agents were found to be either marginally effective or had significant side effects, or the trials with these agents were not adequately controlled, weakening their recommendations (2B−, 2B±, 2C− and 2C± levels).

While some studies reported effectiveness of local anesthetics [procaine (98), lignocaine (99), bupivacaine alone(100)or its combination with magnesium sulfate, NMDA receptor antagonist (101)] in the management of knee pain, they have been not recognized as a standard practice for management of chronic knee pain. However, a recent study has brought a new perspective on use of local anesthetics in management of chronic knee pain. Periarticular branches of the femoral, common peroneal, saphenous, tibial, and obturator nerves (superior lateral, middle, superior medial, inferior lateral, inferior medial, and recurrent tibial genicular nerve) pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. Diagnostic blockade provided a temporary pain relief in patients with knee OA. Under fluoroscopic guidance

lidocaine (2 mL of 2%) was injected at each target site. Responses were recorded as positive if the participant experienced a decrease in numeric pain scores of at least 50% for more than 24 h. Patients with a positive response were offered a radiofrequency neurotomy procedure (102) (2B+ Level).

Of the agents or interventions described in this section only knee lavage was assessed quantitatively in a systematic review fashion. The meta-analysis of six RCTs in 855 patients with OA showed no significant improvement in pain or function (96) (2B− level). A recent Cochrane review found little evidence for a benefit of joint lavage in terms of pain relief at three months, corresponding to a difference in pain scores of 0.3 cm on a 10-cm visual analogue scale between joint lavage and control (97) (2B± level).

Conclusions

The treatment of pain associated with knee OA and RA remains challenging. It is not uncommon that a patient is referred to a pain management specialist due to failure of conventional systemic oral or parenteral treatment. Intraarticular injections of the knee provide an indispensable step in the continuum of management of knee pain from conservative to surgical interventions. It is important to make a distinction between osteoarthritis and rheumatoid arthritis. There is strong evidence that supports the use of intraarticular corticosteroid injections for rheumatoid arthritis (1A+ level), osteoarthritis (1A + level), and juvenile idiopathic arthritis (2C+ level), leading to significant pain relief and functional improvement for months up to one year. Triamcinolone hexacetonide offers an advantage over triamcinolone acetonide and is the steroid of choice (2B+ level). Intraarticular injection of hyaluronate may provide longer pain relief than steroid injection in osteoarthritis (2B+ level) and can also be effective for rheumatoid arthritis (1A+ level). Botulinum toxin Type A injection is effective in reducing arthritic knee pain and so is tropisetron and tanezumab (all at 2B+ level). Other agents, such as rAAV2-TNFR:Fc, SB-210396/CE 9.1, and various radioisotopes, have provided various degrees of success, but their long-term safety and efficacy remains to be determined.

Acknowledgments

This work is supported in part by grants from the National Institutes of Health (NIH/NINDS R01 NS052372) and the Department of Defense (DOD Grant ID# 10669042) to Jianguo Cheng. None of the authors, Olivia Cheng, Dmitri Souzdalnitski, Bruce Vrooman, or Jianguo Cheng or their immediate families has any actual or potential commercial associations that might create a conflict of interest in connection with this manuscript. Olivia T. Cheng was a summer student of Duke University.

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Table 1

Summary of Evidence Scores and Implications for Recommendation*

Score	Description	Implication
1A+	Effectiveness demonstrated in various RCTs** of good quality. The benefits clearly outweigh risk and burdens	Positive recommendation
1B+	One RCT or more RCTs with methodological weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens	
2B+	One or more RCTs with methodological weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens	
2B±	Multiple RCTs, with methodological weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens.	Considered, preferably study-related
2C+	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens	
0	There is no literature or there are case reports available, but these are insufficient to suggest effectiveness and/or safety. These treatments should only be applied in relation to studies	Only study- related
2C−	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefits	Negative recommendation outweigh the benefit
2B−	One or more RCTs with methodological weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens	
2A−	RCT of a good quality which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefits	

*From Van Boxem K, Cheng J, Patijn J, van Kleef M, Lataster A, Mekhail N, Van Zundert J. 11. Lumbosacral radicular pain. *Pain Pract.* 2010;10:339–58.

**RCT=randomized controlled trial.

Table 2

Knee injections for osteoarthritis

Agents	Level of evidence	References	Types of study	Sample size	Comments
Corticosteroid	**1A+**	Godwin M, Dawes M. 2004[12]	Systematic review with meta-analysis.	5 RCTs; n=312	Beneficial effects last 3 to 4 weeks.
		Arroll B, Goodyear-Smith F. 2004[13]	Systematic review with meta-analysis	10 RCTs; n=317	Short term benefit (~2 weeks); Longer term response (16–24 weeks) shown only in the high quality studies.
Hyaluronate *	**2B+**	Bannuru RR, et al.2009[30] Bellamy N, et al. 2006[31] Medina JM, et al. 2006[32] Modawal A, et al. 2005[33] Wang CT, et al. 2004[34] Arrich J, et al. 2005[35] Lo GH, et al. 2003[36] Zhang W, et al. 2008[37]	Systematic reviews Review of practice guidelines	7 systematic reviews 10 practice guidelines	Beneficial effects ~3 months. 5 recent systematic reviews support its use; 2 reviews did not find positive effects; Positive recommendation in 9 out 10 guidelines
	2B±	Altman, et al.2009[40]	RCT	n=588	53% pain reduction in hyaluronate group at 26 weeks; 38% pain reduction in saline control group.
	2B−	Jorgensen A, et al. 2010[41]	RCT	n=337	No difference from placebo at 1 year follow up.
Tanezumab (a humanized NGF monoclonal antibody)	**2B+**	Lane NE, et al. 2010[73]	RCT	n=450	Positive response rate 74–93% at 4 month fellow-up
Tropisetron (5-HT$_3$ receptor antagonist)	**2B+**	Samborski W, et al. 2004[75]	RCT	n=34 (18 RA, 16 OA)	Equally effective as corticosteroid
Morphine	**2B+**	Stein A, et al. 1999[72]	RCT	n=44	Equally effective as corticosteroid providing short term pain relief
Platelet-rich plasma (PRP)	**2C+**	Kon E, et al. 2010[74]	Prospective case - series	n=91	Clinical improvement at 6 month follow up

* The discrepancies in the levels of evidence may be explained by the differences in outcome measures such as the duration of clinical improvement.

NGF=nerve growth factor; OA=osteoarthritis; RA=rheumatoid arthritis; RCT=randomized controlled trial

Table 3

Knee Injections for rheumatoid arthritis

Agents	Level of evidence	References	Types of study	Sample size (n)	Comments
Corticosteroids	**1A+**	Wallen M., Gillies D. 2006[11]	*Systematic Reviews.*	5 RCTs; n=346	Improvement up to 22 weeks; No evidence of harm
Hyaluronate	**1A+**	Saito S, Kotake S. 2009[45]	Systematic review with meta-analysis	5 RCT; n=720	Reliable pain reduction and reduction of inflammation
Radioisotopes					For rheumatoid synovitis refractory to steroid injection
90Yttrium	**1A+**	van der Zant FM, et al. 2009[48]	Systematic review with meta-analysis	11 studies included in meta-analysis; n=342	Significant pain relief at 6 month with success rates of 24–100%
188Re-ti-colloid	**2C+**	Lee EB, et al. 2003[49] Shin K, et al. 2007[50]	Retrospective observational studies	n=21 n=16	Significant clinical and radiographic improvement at 12 month or 6 month after therapy
Samarium-153 in combination with corticosteroid	**2B−**	O'Duffy EK, et al. 1999[54]	RCT	n=60	Chronic arthritis, mainly rheumatoid arthritis; not superior to corticosteroid alone
Botulinum toxin type A (BoNT/A)	**2B+**	Singh JA, et al. 2010[57]	RCT	n=54	For chronic arthritis; Significant clinical improvement at up to 4 months
Tropisetron (5-HT_3 receptor antagonist)	**2B+**	Samborski W, et al. 2004[75]	RCT	n=34 (18 RA, 16 OA)	Equally effective as corticosteroid
SB-210396/CE 9.1 (an anti-CD4 monoclonal antibody)	**2B+**	Veale DJ, et al. 1999[76]	RCT	n=13	Improvement of MRI, arthroscopic, and histological imaging
Immunoglobulin G (IgG)	**2B−**	Bagge E, et al. 1996[77]	RCT	n=11	No clinical improvement

OA=osteoarthritis; RA=rheumatoid arthritis; RCT=randomized controlled trial