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Anesthesiology Clin
25 (2007) 853–862

ANESTHESIOLOGY
CLINICS

Intra-Articular Injections

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Intra-articular injections are one method that physicians may use to treat joint pain. Corticosteroids were the first substances to be injected commonly into the intra-articular space. In the 1950s, corticosteroids were found to lower indicators of the inflammatory response, including the interarticular leukocyte count [1,2]. The indications and effectiveness of intra-articular steroid injections have been debated since their introduction. More recently, viscosupplementation has gained popularity. Local anesthetics also have become common additions to intra-articular injections. Anesthesiologists and orthopedic surgeons have started to explore the use of intra-articular opiates for postoperative analgesia.

Injections for chronic joint pain

Steroid injections

Joint aspiration was described as early as the 1930s. The first intra-articular injectates, which yielded little benefit, were formalin and glycerin, lipodol, lactic acid, and petroleum jelly [3,4]. Hollander [5,6] attempted joint injections with hydrocortisone acetate and found that his patients had a much better clinical response in a series of more than 100,000 injections

A version of this article originally appeared in the 91:2 issue of Medical Clinics of North America.

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1932-2275/07/$ - see front matter
doi:10.1016/j.anclin.2007.07.002 *anesthesiology.theclinics.com*

in 4000 patients. From the 1950s to the present, physicians have used corticosteroid injections routinely to treat joint pain.

Clinical efficacy has been shown for intra-articular injections of steroids in the treatment of rheumatoid arthritis. In a randomized study, patients who were treated with intra-articular injections demonstrated significantly better pain control and range of motion than did those who were treated with mini-pulse systemic steroids. Patient evaluation of disease activity, tender joint count, blood pressure, side effects, calls to the physician, and hospital visits were significantly better ($P < .05$) for those who were treated with intra-articular steroids [7].

Mechanism of action of intra-articular steroid injections

Steroids possess anti-inflammatory properties. On the cellular level, steroids are highly lipophilic and are believed to bind to the cell's nucleus. It is believed that steroids act by altering transcription. Intra-articular steroids seem to reduce the number of lymphocytes, macrophages, and mast cells [8,9]; this, in turn, reduces phagocytosis, lysosomal enzyme release, and the release of inflammatory mediators [1]. Inflammation is reduced, particularly through reductions in the release of interleukin-1, leukotrienes, and prostaglandins [10,11]. With the reduction of these inflammatory mediators, pain symptoms often are improved.

Because they are injected locally, intra-articular steroids avoid most of the systemic effects of oral steroids, including muscle weakness, skin thinning resulting in easy bruising, peptic ulceration, and aggravation of diabetes.

Skin preparation

Skin preparation is as individualized as that seen for surgical site preparation. In a survey of orthopedists and rheumatologists, approximately half used alcohol swabs and the other half used chlorhexidine or povidine-iodine. Less than 20% used sterile towels to isolate the injection site, and only 32.5% of respondents used sterile gloves [12]. The authors recommend preparation with alcohol followed by preparation with Betadine and the use of sterile gloves.

Choice of steroid

Based strictly on chemical structure, the duration of effect should be inversely proportional to the solubility of the steroid (Table 1). There have been conflicting studies on the duration of action of various steroids. Little data exist touting the true efficacy of one agent over another. In most cases, the choice of steroid is related to the personal preference of the physician rather than true science. In a survey performed on members of the 1994 American College of Rheumatology, approximately one third favored

Table 1
Steroid solubility

Steroid	Solubility (% wt/vol)
Hydrocortisone acetate	0.002
Methylprednisolone acetate	0.001
Prednisolone tebutate	0.001
Triamcinolone acetate	0.004
Triamcinolone hexacetonide	0.0002

methylprednisolone, one third favored triamcinolone hexacetonide, and one fifth favored triamcinolone acetonide [9,13].

Use of local anesthetic

At times, local anesthetics (eg, lidocaine) are combined with the steroid. Some physicians contend that the local agent dilutes the steroid crystals, but it is unclear whether this process has any impact on the effect of the steroid. Lidocaine may have a transient anti-inflammatory effect in and of itself [14,15].

Adverse reactions

The most obvious concern about intra-articular injections is infection; however, few orthopedists and rheumatologists have encountered a case of poststeroid septic arthritis [12]. Avoidance of this complication depends on strict adherence to sterile technique. Suspicion of an intra-articular infection or an overlying soft tissue infection contraindicates the injection of a joint with corticosteroid. Other contraindications include a local fracture of total joint. Recent reports found infection rates of between 1 in 3000 and 1 in 50,000 [12]. *Staphylococcus aureus* is the most common infecting organism [12,16].

Mild local reactions do occur after injection. Postinjection flares occurred in about 2% to 6% of patients and were believed to result from chemical synovitis in response to the injected crystals [17]. Facial flushing may be seen in up to 15% of patients, mostly in women [8]. Skin or fat atrophy may be observed at the actual site of needle entry [17]. There is some concern regarding the use of intra-articular steroid injections in the diabetic population. Transient increases in blood glucose may be seen in patients receiving corticosteroid injections; however, in a study of diabetic patients who received soft tissue injections of methylprednisolone acetate, there was no detectable effect on blood glucose levels in the 14 days after injection [18]. Intra-articular steroids also transiently affect the hypothalamic–pituitary–adrenal axis. These changes, which include a 21.5% reduction in serum cortisol levels, typically normalize within 3 days, although an episode of Cushing's syndrome was reported [19,20].

Joint destruction after repetitive injections is a common concern. Animal studies have been suggestive of damage to articular cartilage because of

intra-articular steroid injections; however, there are no human data to corroborate this claim [10]. Because of fear of possible joint destruction, many physicians recommend 3 months between injections of the same joint [13,21].

Clinical trials

One of the largest clinical trials of intra-articular steroid injections was done in the 1950s by Hollander [5,6]. Hydrocortisone injections of 1034 knees with osteoarthritis revealed an 80% success rate. Since that time, a multitude of studies proved the excellent short-term pain relief (1–4 weeks) gained from injected corticosteroids [21]. Longer-term results were not proved in consecutive studies; however, the short-term pain relief may allow the patient to return to baseline function and improve one's ability to perform physical therapy [22,23].

An adjunct to the success of steroid treatment in the patient who has an effusion may be the aspiration of that effusion. Eighty-four patients who had osteoarthritis were randomized to receive triamcinolone hexacetonide or placebo. Patients who received the steroid reported a statistically significant improvement in pain, distance walked in 1 minute, and Health Assessment Questionnaire score. Among patients who were treated with steroids, those who had an effusion that was aspirated at the time of injection showed greater improvement ($P < .05$) [24]. Joint lavage similarly improved pain and function if performed at the time of steroid injection [25].

Hyaluronic acid

Intra-articular steroids are not the only materials that are injected intra-articularly in the treatment of osteoarthritis. A randomized, placebo-controlled study compared more than 100 patients who received hyaluronic acid, corticosteroid (methylprednisolone acetate), or isotonic saline. These injections were placed with the aid of ultrasound. Injections were administered at 14-day intervals, with each patient receiving three injections. Significant improvement was seen at 3 months in the population that was treated with corticosteroid compared with patients who were treated with saline ($P = .006$ at 14 days, $P = .006$ at 28 days, and $P = .58$ at 3 months), whereas improvement in the group that was treated with hyaluronic acid failed to reach statistical significance ($P = .069$ at 14 days, $P = .14$ at 28 days, and $P = .57$ at 3 months). Statistically, there was no significant difference between hyaluronic acid and corticosteroid at any time point ($P > .21$) [26].

Postoperative intra-articular analgesia

The analgesic effects of intra-articular agents in the postoperative period are controversial; however, their use is becoming more common in the

outpatient orthopedic setting [27]. The use of peripheral blocks for extremity surgery requires greater skill in placement and has a potential for significant complications [27]. Arthroscopy has been described as a method for orthopedic improvement with decreased morbidity, but not one of decreased pain [28,29]. Poor pain control may prevent a procedure from being acceptable in an outpatient setting, therefore, postoperative analgesia becomes an important consideration for outpatient surgery centers. Intra-articular analgesia techniques are used most commonly for knee and shoulder surgery. With some debate, intra-articular administration of local agents has proven effective for knee arthroscopy [30–38]; however, pain control for the shoulder has proven a greater task. Severe pain scores have been reported for even the most minor shoulder procedures [39].

Local agents

Most anesthesiologists and orthopedic surgeons select bupivacaine because of its long duration of action. This does not preclude the use of other local agents. The literature on the use of intra-articular local anesthetics includes numerous studies, but it is difficult to interpret because of the use of confounding agents, such as intra-articular opiates, clonidine, and nonsteroidals. A large number of these studies also is flawed with regard to study design, data collection, and reporting. A systematic review of double-blind, randomized, controlled trials that compared intra-articular local with placebo or no intervention and found a statistically significant improved pain after intra-articular local in pain scores. Pain scores were significantly lower in the treatment group and the amount of supplemental analgesics requested was reduced by 10% to 50%. The presence of hemarthrosis, which can increase the level of pain and decrease the concentration of local agents, is another factor that may alter the activity of intra-articular local analgesia [37]. Although the data from this review seem to indicate that intra-articular local analgesia is only mildly effective, its use in the outpatient orthopedic setting is a popular and safe adjuvant [40].

A continuous infusion of intra-articular analgesia was examined. In a prospective randomized trial of 50 subjects who underwent acromioplasty and rotator cuff repair and received a multiorifice catheter placed in the subacromial space, no statistically significant difference in pain scores or patient-controlled analgesic use was detected [41].

Opiates

Opioid receptors have been discovered in the peripheral nervous system. Mu, delta, and kappa receptors were found on peripheral nerves [37,42]. The effectiveness of opiates in inflamed tissues has been explained by a disruption in the perineurium, allowing for easier access of opioids to neuronal receptors. This also may be associated with an unmasking or up-regulation of inactive opiate receptors [37,43]. It was proposed that the effects of

intra-articular morphine might simply be due to systemic absorption; however, the plasma concentration achieved from an intra-articular injection would be far too low for a systemic effect to be observed [37]. Within the joint itself, the relative concentration is high.

Kalso and colleagues [44] reviewed 36 randomized controlled trials. Four of the six studies that compared opiates with placebo found greater efficacy for intra-articular morphine. Four of the six studies that compared intra-articular morphine with intravenous or intramuscular morphine showed greater efficacy for intra-articular morphine. Several dosages were used with varying effects in the literature reviewed. Specifically, the minimum dose tested (0.5 mg) did not show efficacy, but a dose of 1 mg did. No greater effect was found when a dose of 1 mg was compared with 2 mg [44,45].

In a review by Gupta and colleagues [46], a meta-analysis was completed on the pooled data of 19 prospective, placebo-controlled, randomized studies in which intra-articular morphine was used. Within these studies, visual analog scores were collected at the early phase (0–2 hours), the intermediate phase (2–6 hours), and the late phase (6–24 hours). This analysis concluded that although no clear dose-response effect was seen, a definite, but mild, analgesic effect was present.

Another recent review is a bit more skeptical. Rosseland and colleagues reviewed randomized controlled trials that involved the use of intra-articular morphine [29]. In the 43 publications included, some of which were included in the reviews by Kalso and colleagues [44] and Gupta and colleagues [46], 23 were believed to be of low scientific quality with poor randomization and blinding or unsound statistics. Thirteen were believed to have usable information; however, four of the positive outcomes were believed to be due to the uneven distribution of patients whose natural course was low postoperative pain. The only randomized control trial that Rosseland believed was adequate was negative [47].

Clonidine

Intra-articular clonidine also has been investigated. Clonidine is an α-agonist that was shown to prolong the duration of local anesthetics. In a controlled study, 40 patients who underwent knee arthroscopy were randomized to receive intra-articular clonidine in combination with 1 mg of morphine. Patients who received clonidine had significantly longer analgesia durations [37].

Many physicians who participate in outpatient orthopedic surgery recommend a multimodal approach consisting of intra-articular agents, including local analgesia, an opiate, and an adjunct (eg, clonidine) [37]. The specifics of the injectate are left to the individual. Local analgesia seems to be helpful early in the postoperative period (2-4 hours) to prevent a deleterious physiologic pain response. Intra-articular morphine may be more

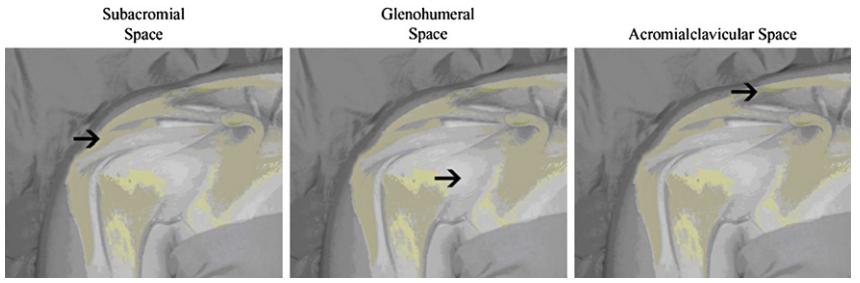

Fig. 1. Spaces in the shoulder that may be treated by an intra-articular injection.

helpful in the hours afterward. In general, the use of pre-emptive and multimodal analgesia is important to abate postoperative pain, with an emphasis on minimizing systemic narcotic analgesia, which has the deleterious effects of respiratory depression, sedation, nausea, puritis, and delayed discharge [37].

Techniques to improve placement

Figs. 1 and 2 illustrate the anatomic locations for injections into the shoulder and knee. It is truly with repetition that the physician becomes facile with most intra-articular injections. Image guidance with the aid of ultrasound or fluoroscopy is a valuable tool to help access difficult joints, such as the hip. Fluoroscopy and a radiopaque tracer allow for documented delivery of an agent into a joint. Aspiration of synovial fluid before injection of a steroid is one method that may allow for improved accuracy.

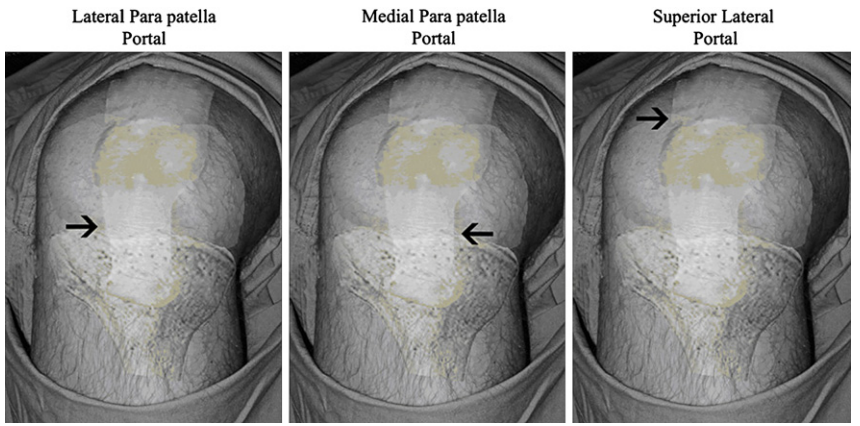

Fig. 2. Different approaches used to access the knee for an intra-articular injection.

One study examined this question. A recent article assessed the accuracy of needle placement in the intra-articular space of the knee using three common knee joint portals. The investigators documented the location of the injected fluid by fluoroscopic imaging. They found far more success with a lateral midpatellar injection than with either of the other injection portals [47].

Summary

Intra-articular injections provide physicians with one modality to treat chronic or acute joint pain. Whatever method is chosen, careful attention to the anatomic landmarks and experience are critical to the successful placement of an intra-articular injection. Intra-articular steroid injections have been used for management of inflammatory joint diseases, such as arthritis. Occasionally, local anesthetics are injected in combination with the steroids. New studies found that intra-articular injections may be helpful for the management of postoperative pain, particularly with the use of opiates.

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