Intra-Articular Corticosteroids: An Investigation of Uses, Benefits, and Risks

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Submitted as required in fulfillment for the degree of:
MASTER OF NURSING
Washington State University
Intercollegiate Center for Nursing Education
May, 1999
To the faculty of Washington State University:

The members of the Committee selected to examine the project of Kathi M. Stevens find it satisfactory and recommend that it be accepted.

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Acknowledgments

I would like to express my gratitude to Renee, as my committee chair, for her adroit encouragement and critique. I thank her, also, for editing expertise which guided this paper to completion. I thank Josette for nurturing the emerging practitioner in me and prompting the leap “off the fence”. I appreciate Lorna for starting the process with the case studies in pharmacology, teaching us the steps.

I would like to thank Pam Anderson, ARNP, for taking the time in a health maintenance visit to give referrals and encouragement for pursuing my degree. Her professionalism, expertise, and obvious enjoyment of her work were a catalyst to my process and have refreshed me during the struggle.

I wish to recognize Myron Stevens, my father, who taught me the questions to ask for a thorough history. He introduced me to “when did it start, what have you done, what makes it better, what makes it worse, and has this happened before” for diagnosing mechanical ills. Little did I realize these would be the basis for my profession.
Intra-articular Corticosteroids: an investigation of uses, benefits, and risks

By
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May, 1999

Abstract

Chair: Dr. Renee Hoeksel

Injectible corticosteroids have been investigated as a treatment of musculoskeletal pain since before the 1950’s (Hench, Kendall, Slocumb, & Polley, 1949). Intra-articular administration affords patients varying levels and periods of symptom relief. Duration and extent of relief are influenced by length of symptomatology and frequency of recurrence. Untoward effects may be experienced either locally, systemically, or even allergic in nature (Alexiou, Kau, Luppa, & Arnold, 1998; Downs, Lear, & Kennedy, 1998).

Glucocorticoids, a class of naturally occurring corticosteroids, are important in the body’s management of carbohydrates, proteins, fats, blood pressure, sodium and potassium balance, and most importantly, the reduction of inflammation. Many are synthetically manufactured for a variety of uses (Mosby's Medical, Nursing, and Allied Health Dictionary, 1994). The purpose of this paper is to review advantages of intra-articular use including appropriate protocols and to identify the specific side effects with their risk of occurrence. Although many have studied intra-articular corticosteroid use (presenting a range of variables and methods of study), standards for dosing volumes and concentrations, and for measuring disability, pain, and status changes have not been established. Therefore, comparison among studies is difficult. Effects and outcomes have not been investigated in a manner that allows risks and benefits to be consistently determined.
# Table of Contents

Acknowledgments ........................................................................................................ 3

Abstract .................................................................................................................................. 4

Table of contents .................................................................................................................. 5

List of Tables ......................................................................................................................... 6

Introduction ............................................................................................................................ 7

Indications and outcomes ....................................................................................................... 8

Side Effect .............................................................................................................................. 14

Conclusions ............................................................................................................................ 19

References .............................................................................................................................. 21
List of Tables

Table 1 ......................................................................................................................... 28
Table 2 ......................................................................................................................... 29
Introduction

Intra-articular corticosteroids: An investigation of uses, benefits, and risks.

Injectable corticosteroids have been investigated as a treatment of musculoskeletal pain since before the 1950s (Hench, et al., 1949). Intra-articular administration affords patients varying levels and periods of symptom relief. Duration and extent of relief are influenced by length of symptomatology and frequency of recurrence. Untoward effects may be experienced either locally, systemically, or even allergic in nature (Alexiou, et al., 1998; Downs, et al, 1998). These untoward effects, when reported, range from transient pain at injection site (Hochberg, et al., 1997) erythema, facial flushing (Caldwell, 1996; Stahl, & Kauffman, 1997) or dermal atrophy (Cassidy, & Bole, 1966; Gottlieb, Pennys, & Brown, 1978; Jones, et al., 1993; Louis, Hankin, & Eckenrode, 1986) to fluctuations in blood pressure, blood glucose (Hench, et al.; Koehler, Urowitz, Murray, & Killinger, 1974) and menstrual cycle (Carson, Daane, Lee, Tredway, & Wallin, 1977; Mens, De Wolf, Berkhout, & Stam, 1998).

Glucocorticoids, a class of naturally occurring corticosteroids, are important in the body’s management of carbohydrates, proteins, fats, blood pressure, sodium and potassium balance, and most importantly, the reduction of inflammation. Many are synthetically manufactured for a variety of uses (Mosby’s Medical, Nursing, & Allied Health Dictionary, 1994). The purpose of this paper is to review advantages of intra-articular use including appropriate protocols and to identify the specific side effects with their risk of occurrence. This information adds to the primary care providers’ arsenal for making evidence-based choices in treating and educating clients.
Indications and outcomes

The first step for the practitioner is determining who best benefits from intra-articular corticosteroid injection. Numerous factors appear to contribute to defining a population amenable for intra-articular corticosteroid therapy. Rheumatoid arthritic affected joints were some of the first injected along with osteoarthritis, and bursitis (Hench, et al., 1949; Hollander, Brown, Jessar, & Brown, 1951). Variance emerges regarding time since onset of pain, amount of inflammation, extent of dysmobility (Croft, Pope, & Silman, 1996; Holt, Keene, Graf, & Helwig, 1993), and chronicity or repeat episodes of symptoms. Inconsistent reporting in the literature of clinical indications for injection and evaluation of efficacy is further complicated by a lack of research data correlated with patient outcomes (see Table 1).

There is considerable variance in the research literature regarding diagnostic criteria, disease indices for inclusion or exclusion, and reporting. Table 2 illustrates this variance in time since onset of symptoms, previous intra-articular therapy, and chronicity of joint pain. It also indicates, in the last column, the inconsistent manner of diagnostics used for inclusion into studies. A lack of uniformity in subjects arouses concerns of an undefined impact on outcomes (Green, Bunchbinder, Glazier, & Forbes, 1998).

Delay in definitive treatment may be due to differences in practitioners recognizing pathology or in management such as utilizing electrophysiological testing (Pal, Morris, Keenan, & Mangion, 1997). Inappropriate patients may receive treatment (Hochberg, et al., 1995) and be reported as treatment failures. Misdiagnosing can lead to inappropriately placed injection that will provide no relief for a truly treatable problem (Caldwell, 1996; Drugs and Therapy Perspectives, 1997; Jones, et al., 1993).
Reduction or elimination of pain, improved mobility, and improved dysfunction in joints are treatment goals in the utilization of intra-articular, intracapsular, and interdermal corticosteroids. Treatment goal measurement can be made in duration of pain relief, amount of relief, number of injections required, change in extent of disability, length of relief from disability, or a combination of these. Great variability exists in treatment approaches including the instruments available for and timing of these outcome evaluations.

Duration of symptom relief was not studied in isolation. Many of the studies mention timing of evaluation of outcomes (Table 1), yet no standardization exists (Eustace, Brophy, Gibney, Bresnihan, & FitzGerald, 1997; Louis, et al., 1986; Creamer, 1997; Winters, Stobel, Groenier, Arendzen, & Meyboom-de Jong, 1997; Goh, Over, Daroszewska, Whitehouse, & Bucknall, 1997; Stahl, & Kauffinan, 1997). An example is (Stahl, & Kauffman) follow-up at six weeks, three months, and one year for pain in 60 elbows with medial epicondylitis. In this double bind study, one half of subjects were injected with methylprednisolone. It was concluded that pain was substantially and more quickly reduced in the experimental group within the first six weeks. No differences of any significance were detected by three months nor at one year.

Pain intensity is frequently measured on visual analog scales. The literature reveals little uniformity of instruments for measuring pain. In addition, there are modifications to incorporate disability or enhancements of supplemental questionnaires. A ten-point intensity scale was employed in four studies (Stahl, & Kaufman, 1997; Adebajo, Nash, & Hazleman, 1990; Bradley, Brandt, Katz, Kalasinski, and Ryan, 1991; Eustace, et al., 1997). A four-point “pain phase” scale (Stahl) was used to relate the amount pain to activity limits in patients treated for medial epicondylitis. A zero to three rating of functional limitation (Adebajo) was added for evaluation of knee osteoarthritis. A five-point, descriptive scale rating (Eustace) was used in determining benefit of injection for shoulder pain.
Another shoulder study utilized a pain score apparently linking pain and disability to outcomes. If residual pain did not interfere with functioning, treatment was considered a cure (Graber, 1997; Van der Wendt, Koes, et al., 1998). An 100-point scale was used for pain and stiffness evaluation in fingers (Helliwell, 1997). A five-point global rating scale (pain and disability), added at follow-up exam, evaluated maximum and current benefits in a study of shoulder treatment (Eustace, et al., 1997). Pain was assessed in a single blind, randomized comparison of treatments for shoulder complaints in 198 patients by combining a questionnaire with a numerical pain scale which was converted to a single point range (Winters, et al., 1997). Pain levels associated with passive range of motion, stair climbing, and walking were recorded as a zero to three score used to evaluate inflammation after injection of knees. A further disability component was added by subjective reporting of ability to conduct daily at home and outside the home activities. This, also, was recorded on a zero to three scale (Cuchacovich, et al., 1988). The most exhaustive study used the Oswestry Low Back Pain Disability Questionnaire, a visual analog pain score, the McGill pain intensity score, and a sickness impact profile in evaluation of epidural injections for sciatica due to herniated nucleus pulposus evaluation (Carette, et al., 1997).

Variability in instruments and parameters for defining clinical outcomes of steroid injections were directly addressed by two studies (Green, et al., 1998.; van der Windt, Koes, et al., 1998). An evaluation of randomized controlled trials with blinded assessment of outcomes found no standard definitions were used and exclusion criteria varied widely with conflicting criteria often defining the same condition in different trials. Small effect sizes and lack of disability scores were found which suggest questionable benefit of treatment. A third study (Van der Windt, et al., 1998-a) examined the Shoulder Disability Questionnaire, that was developed for ease of administration and adaptability to randomized trials. This questionnaire is used in conjunction with a pain severity scale to evaluate the subjective issue of pain.
Some studies omitted reporting the measurement tool or scale used, while others attempted to develop specific methods. Improvement and freedom from symptoms were the only recordings made in a retrospective evaluation of 23 patients after receiving corticosteroid injection under arthrography with shoulder joint involvement (Goh, et al., 1997). Examination for osteitis pubis in athletes in a retrospective study of intra-articular injection does not indicate any standardized tool used for scoring pain responses (Holt, et al, 1993). Guidelines in the literature for management of arthropathies and arthralgias are reported without giving any types or examples of methods for evaluating patients on intake, during treatment, or for outcomes (Hochberg, et al., 1995). No method of measuring pain was defined in a focus study using synovial biopsies from knees post injection (Firestein, Paine & Littman, 1991). The study attempted to develop an inflammation score with great detail describing gene expression positively correlated with reduced and resolved pain. A study of knee inflammation in response to intra-articular corticosteroids developed a novel grading system (Bradley, et al., 1991). The examining doctor recorded an assessment of fluid and distortion of joint contours as one to three. A unique method for measuring pain was employed in a retrospective study of Achilles tendons (Read, & Motto, 1992). The number of hops until onset of pain was the determinant for measuring pain and disability. This was correlated to a particular rehabilitation program with fitness, or outcome, defined as “match ready” in the preferred sport.

Pain may not be the only or best indicator to record for response to injected corticosteroids. Although significant decrease in pain is noted up to three weeks, other longer term benefits may be present that pain measuring tools may not be evaluating (Creamer, 1997; Koehler, et al., 1974). Osteoarthritic disorders are a heterogeneous group that can have varying degrees and periods of inflammation that respond to steroid injections. It is also thought that better ways to target these inflammatory episodes in the disease process could be developed if methods or tests for identifying
unspecified benefits to steroid injections were in place. Creamer (1997) postulated that genetic markers from the synovium may provide indices for flair periods in the future. Timing injections to flares could provide more than random success in the management of this wide spread disease.

Another approach was the attempt toward developing a synovial inflammation marker (Firestein, et al., 1991) in addition to subjective pain scores for evaluating rheumatoid arthritis and osteoarthritis synovium.

Physical exam is an integral part of patient evaluation, yet a wide range of reporting and methodology is encountered in the research literature. The reviewed literature included a range of undefined clinical exams, symptomatology evaluations of shoulders (Goh, et al., 1997) to detailed, concise reports of sciatica (Carrette, et al., 1997) and osteitis pubis (Holt, et al., 1995). Quantifying examinations of active and passive range of movement were conducted using a pendulum goniometer measuring to 5 degrees for shoulders (Adebajo, et al., 1990) and to the end of range for fingers (Helliwell, et al., 1997). Joint circumference measurements were used as an objective parameter to indicate improvement after injections in finger and knee joints (Cuchacovicb, et al., 1988; Helliwell, 1997). This type of circumferencial measurement is not reproducible for shoulders. There was no discussion in the literature of how this measurement was benchmarked indicating relationships to the current pain/disability episode or to a baseline. Inconsistency of reporting what specific exams are utilized also exists (Green, et al., 1998). This range of methods and reporting is illustrated in column 5, Table 2.

Accurate placement of the injection is a factor in treatment efficacy. Shoulder injections guided by arthrography resulted in higher success rates than expected (Goh, et al., 1997). A six-week study to evaluate accuracy of injection placement and outcome of intra-articular methylprednisolone in a number of joints found a significant inaccuracy rate. This was not statistically correlated to poorer
outcomes (Jones, et al., 1993). A subsequent study of shoulder injections of 38 subjects resulted in 24 inaccurately placed injections with positive benefit reported in only 7% of these. The accurately placed injection group reported 28.6% with “great” benefit (Eustace, et al., 1997). Variable results of steroid injections for carpal tunnel syndrome were, also, attributed to placement accuracy (Pal, et al., 1997).

One study declares that “no injections were made into the tendons or glenohumeral joints” without stating how this was verified (Adebajo, et al., 1990). In contrast, a shoulder pain trial listed a limitation of the study as no confirmation of injection placement (Graber, 1997). Standards for reporting injection accuracy or how to relate placement to positive outcomes are noted as lacking (Croft, et al., 1996). In summary, there are currently no “gold standards” for evaluating clinical outcomes, yet these injections are accepted clinical procedures for a wide variety of musculoskeletal indications.
Side Effects

Complications are reported as relatively infrequent with regional therapy (Louis, et al., 1986). Intra-articular corticosteroids may reduce the magnitude and incidence of systemic effects much the same as postulated with parenteral administration of androgens (anabolic steroid) and estrogens producing less changes than oral routes (Henkin, Yaakov, Como, & Oberman, 1992). Limited and varied lengths for follow-up (see Table 1) may, also, impact the thorough investigation of side effects (Cuchacovich, et al., 1988).

As early as 1949 investigators of intra-articular corticosteroid use noted that volume, milligram dosing, and accuracy can contribute to untoward effects (Hollander, et al., 1951; Hench, et al., 1949). Many reports record dosages and volumes used in the study; some also note that this is a factor or possible contribution to outcomes and side effects. The potency of preparation is not altered by route of administration. There is, however, a scarcity of comparative literature on these factors (Fredberg, 1997). The importance of milligram versus milliliter dosing must be attended to to avoid deposition of high doses of steroid which can also be deleterious. Potency dose equivalent tables must be examined carefully if they are for oral administration routes as intra-articular or intramuscular injection may differ greatly contributing to the risk of inadvertent local overdosing or inappropriate volume (Louis, et al., 1986). A larger milligram dose does not correlate with greater symptomatic amelioration or prolongation of relief (Cassidy, & Bole, 1966; Hollander, et al., 1951). The volume must also be considered for the site being injected. Use of an inappropriate volume for the injected space may contribute to extravasation and subsequent damage in surrounding tissue. No table of optimal volumes or comparative studies of these were found. An inappropriately placed injection can contribute to untoward effects. Post-injection neuritis is possible if a larger nerve is injected (Fredberg, 1997).
Dermal changes may, in part, be the result of injection accuracy (Goh, et al., 1997 and Jones, et al., 1993).

Assessing side effects is complex. A 1997 study found undefined side effects as a constraint to use of injectable steroids by rheumatologists and these were not pursued as part of the study (Pal, et al., 1997). Adebajo, and others (1990) report no side effects other than post injection discomfort. It is not stated what was asked or how the information was elicited. Similarly, Eustace, and others (1997) state that patients were asked for any side effects. Only pain at the site, which resolved was noted; no numbers are given. A prospective, randomized, double-blind study of fifty-eight patients (sixty elbows) to evaluate short and long term effects of local injection of methylprednisolone in the treatment of epicondylitis reported one female participant as experiencing facial flushing within twenty four hours of injection, which subsequently resolved (Stahl, & Kauffmann, 1997). Participants are followed up by interviews and physical exam for up to one year for local fat atrophy, depigmentation, disruption of muscle origin, post-injection flare, facial flushing, and iatrogenic infection and none were found. Postinjection flare and local pain are recorded as transient effects(Hochberg, et al., 1995; Hollander, et al., 1951), lasting only 24 hours (Fredberg, 1997). Local site discomfort or flare resolving in 12 hours to five days (Kirschner, 1998) have been documented. The occurrence has been related to crystalline suspensions, particularly the triamcinolones (Drugs and Therapy Perspectives, 1997).

Most commonly noted side effects of injections are local fatty, dermal, and soft tissue changes. Their incidence is reported at less than 1%, receding over time and of little harm (Louis, et al., 1986). These changes may become apparent as early as one month after injection and last up to four years (Cassidy, & Bole, 1966; Gottlieb, et al., 1978; Louis, et al., 1986). A less common skin change is dermal atrophy overlying lymphatic vessels radiating from injection sites (Gottlieb). Telangiectasia,
transparency, and hyperesthesia or hypoesthesia may accompany atrophy of overlying skin (Fredberg, 1997).

Allergic reactions to corticosteroids have been documented. Symptoms may include anaphylactic type blood pressure drops, airway compromise involving swollen lips and wheezing. Other types of reactions are erythema of face and trunk, itching, flushing, headache, and feelings of breathlessness and dizziness (Alexiou, et al., 1998; Downs, et al., 1998). Although cortisone allergy is rare (Caldwell, 1996), anaphylaxis is not a theoretical complication and has been carefully documented following interdermal injection (Downs, et al., 1998). Flushing along with headache and rashes is attributed to sensitivity to the vehicle particularly in the triamcinolones (Drugs and Therapy Perspectives, 1997).

Number of injections is of concern in contributing to unwanted effects. Guidelines for management of knee osteoarthritis (Hochberg, et al., 1995) notes that it is recommended, but not well substantiated by published data, that three to four times a year is the maximum number of intra-articular injections as there is concern of possible development of progressive cartilage damage in weight bearing joints (Caldwell, 1996; Drugs and Therapy Perspectives, 1997). The constraint not to use “repeated injections” is made by Louis, and others (1986) when disclosing dermal atrophy after six injections over the radial styloid. A study describing dermal effects after 40 injections in each knee in a three year period attributes the dermal atrophy, possibly, to the repetitive nature of the injections, and also to the potency, and volume of compounds used (Gottlieb, et al., 1978). Up to three epidural injections are used to evaluate corticosteroid treatment for sciatica but there is no data to indicate how this number was chosen (Carette, et al., 1997). Recommendations for treatment of Achilles tendons are as vague as “judicious” use (Read, & Motto, 1992). Triamcinolone can be “repeated as needed”
Intra-articular corticosteroids


None of the authors address how many years injections can be repeated.

Tendon rupture as a consequence of corticosteroid peritendonous injection has been postulated. It is noted that patients with inflammatory disease and the end stage of many chronic sports injuries may suffer such ruptures, but there have not been human prospective, randomized trials (Fredberg, 1997) to confirm this. Tendon weakening and rupture are noted as cautions for inadvertent injection of the collagenous body of a tendon (Drug and Therapy Perspectives, 1997) as this may weaken its structure (Caldwell, 1997). Pure peritendinitis is an inflammatory response that will respond to intra-articular steroids, however, treatment may reduce tensile strength for two to three weeks (Read & Motto, 1992; Wiggins, Fadale, Barrach, Ehrlich, & Walsh, 1994). This side effect may be an omission of using the recommended caution in gradual conditioning back to full activity (Read; Stannard & Bucknell, 1993).

Systemic effects from local, repeated corticosteroid injections are seen. Adrenal cortical suppression, osteoblastic activity, and hypoglycemia are noted (Fredberg, 1997) without percentages of occurrence given. Acetate compounds provide a sustained site effect in the joint as they are only slightly soluble in bodily fluids. There is no direct correlation between biologic half life and plasma half-life (Mosby, Inc., 1997). Differing absorption rates for various compounds which reduce half-life within the joint (Drugs and Therapy Perspectives, 1997), leave the patient vulnerable to systemic effects for differing lengths of time. This systemic absorption is of concern when managing brittle blood glucose or immunologically fragile patients. Elevations in blood glucose are induced by this absorption, therefore, diabetics need to under glycemic control (Caldwell, 1996). Clotting is also noted as being impacted. Caution must be used for those patients on anticoagulant therapy, or those with coagulopathies, as hemorrhage may occur in the joint. Guidelines as to the extent of effects or
percentage of patients affected were not found (Drugs and Therapy Perspectives, 1997). Triglycerides and cholesterol can be increased by corticosteroid therapy (Stanbury, & Graham, 1998), although these may be variable with females generally having more prominent changes (Henkin, et al., 1992).


Menstrual irregularities are encountered as side effects of intra-articular corticosteroid use. The changes may affect onset, duration or amount of flow. Abnormalities are significantly less in women using oral contraceptives (Mens, et al., 1998). The variation in effects may also be attributed to timing of therapy in relation to menstrual cycle. No caution or study was encountered regarding effects on birth control efficacy.
Conclusions

Corticosteroid injections provide relief to numerous persons suffering from musculo-skeletal pain and limitation of movement. Side effects to intra-articular corticosteroid injections exist, yet limited reporting on how to reduce and eliminate their occurrence is available to practitioners (Mosby, 1997; Drugs and Therapy Perspectives, 1997; Fredberg, 1997; Louis, et al., 1986; Goh, et al., 1997). Systemic effects from injected corticosteroids also occur (Fredberg; Caldwell, 1996; USP DI-Vol.II Advice for the Patient, 1997;). Corticosteroids effect many bodily functions and interact with numerous medications (Stanbury & Graham, 1998). This review has been unable to locate severity and frequency documentation in randomized, clinical studies. It is beneficial for practitioners to know risks of triggering or exposing a patient to side effects or interactions and the severity of these when considering and presenting treatment options to clients. Careful documentation of diagnostic criteria, history of complaint and outcomes will contribute to the growth of this body of knowledge.

Standardization of tools for measuring effects and outcomes (Green, et al., 1998; van der Windt, van der Heijden, et al., 1998) is needed to improve evaluation and utilization of interventions. Standardization of technique (Eustace, et al., 1997; Goh, et al., 1997; Caldwell, 1996) along with accurate tools and meticulous diagnoses may yield higher efficacy rates. It is repeatedly documented that early treatment by intra-articular corticosteroids seems to yield better results (Pals, et al., 1997). Definition of “early” needs to be made, while using recognized tools for evaluating results. Patient input on what a positive outcome means must be part of evaluation and consideration for using intra-articular corticosteroids. Correlation needs to be made of duration of pain and disability relief, patient satisfaction with treatment, and the determination of positive outcomes. Meta-analysis of differing painfree periods and related treatments is needed. Actual incidence of side effects must be addressed including systemic effects as patients with concurrent diseases such as diabetes or immunosuppression.
are frequently encountered in today’s patient population. Definition of satisfactory outcome needs to include duration and amount of symptom relief correlating pain and disability. Such studies must then be analyzed against other management modalities for comparative complaints as done by Winters, and others (1997). Only then can they truly help us to elucidate if we are succumbing to giving a drug when physical therapy and/or rest are more efficacious treatments.
References


Intra-articular corticosteroids

Journal of Medicine, 336, 1634-1640.


Intra-articular corticosteroids


Intra-articular corticosteroids


Available: Griffin/Proquest/00207888 [1998,December 3].


### Table 1. Time and Methods of Follow-up

<table>
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<th>Author</th>
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Table 1. * lab = objective, laboratory values given.
** cellular = cellular changes recorded.
~ hop test = study specific test; see text.
^ exam = unspecified.
Table 2. Variability of inclusion criteria

<table>
<thead>
<tr>
<th>Author</th>
<th>Time from onset</th>
<th>Previous IA*</th>
<th>Chronic Pain</th>
<th>Dx. ** method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adebajo</td>
<td>&lt; 3 mo.</td>
<td>none in &lt;3mo</td>
<td>no</td>
<td>exam</td>
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<tr>
<td>Armstrong</td>
<td>unknown</td>
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<td>unknown</td>
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<tr>
<td>Bradley</td>
<td>min. 3 mo.</td>
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<td>xray, exam</td>
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<tr>
<td>Carrette</td>
<td>&gt;4mo, &lt;1yr</td>
<td>&lt;1yr</td>
<td>yes</td>
<td>criteria, exam</td>
</tr>
<tr>
<td>Cassidy</td>
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<tr>
<td>Croft</td>
<td>&gt;1mo, &lt;1yr</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>Cuchacovich</td>
<td>&gt;1yr</td>
<td>yes</td>
<td>unknown</td>
<td>lab, criteria</td>
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<td>&gt;2mo</td>
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<td>Farooqi</td>
<td>varying</td>
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<td>Firestein</td>
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<td>unknown</td>
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<td>undefined criteria</td>
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<td>yes</td>
<td>criteria</td>
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<td>Hench</td>
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<td>no</td>
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<td>up to 3-4per yr</td>
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<td>van der Windt</td>
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Table 2. * intra-articular injection. Does not distinguish how long since last injection, number of previous injections, or if a consistent for total population studied.

**diagnostic method. Criteria = described for the study. Exam = physical exam done for inclusion in study population. Rheumatologist = specialist exam or record review for the study. Dx = stated diagnosis only, without description of methodology or source.