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Darren Scott Pledger
University of North Dakota

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The Effectiveness of Oral Non-Steroidal Anti-Inflammatories Versus Steroid Injections in
Patients with Shoulder Pain.

by
Darren Scott Pledger PT, DPT

Bachelor of Health Science, University of Central Arkansas, 2006
Doctorate of Physical Therapy, University of Central Arkansas, 2009

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Abstract

Shoulder pain is the third most common musculoskeletal complaint in primary care. Therefore, it is important that we have quality evidenced based treatments to guide clinicians in treating shoulder pain. I examined in this review whether corticosteroid injection into the glenohumeral joint or oral NSAIDs was more effective in reducing shoulder pain as well as the side effects associated with each treatment modality. Search methods included the PubMed and Cochrane databases. Only studies comparing corticosteroid injection and oral NSAIDs were included and not each treatment individually. In conclusion, corticosteroid injections into the glenohumeral joint accelerate pain relief but have equal efficacy on long term follow up. Both corticosteroid injections and oral NSAIDs are superior to placebo but one is not superior to the other. Corticosteroid injections were associated with some local side effects with systemic side effects being rare. Oral NSAIDs do have an effect on the gastrointestinal system, kidneys, and cardiovascular system thus they are not recommended for certain patient populations. This study provides a good framework to guide clinicians in the treatment of shoulder pain but further studies need to be done to include a formal physical therapy program and the effect of these treatments on specific shoulder conditions.

Keywords: shoulder pain, NSAID, steroid injection, non-steroidal anti-inflammatories, corticosteroid injections, side effects, adverse reactions

Introduction

Shoulder pain is a very common condition encountered in primary care. Its prevalence is around 34% in the general population and 21% in those over 70 years of age. It accounts for 1.2% of all primary care encounters and is the third most common musculoskeletal complaint behind neck and back pain (Buchbinder, Green, & Youd, 2003). The glenohumeral joint is a complex joint with multiple structures that can be injured leading to a decrease in function. Managing shoulder pain can be difficult, but it is necessary in order to restore function and quality of life for our patients. This literature review's goal is to answer the question of which treatment strategy, oral non-steroidal anti-inflammatories (NSAIDs) or corticosteroid injections into the glenohumeral joint, is the most effective at reducing shoulder pain. As with any medical treatment, providers need to be aware of the risks that are associated with that treatment in order to make a good clinical decision that results in a positive outcome. This review will examine the efficacy of oral NSAIDs and corticosteroid injections as well as possible side effects of each treatment in order to assist clinicians in making an appropriate treatment decision.

Statement of the Problem

The fact that shoulder pain is the third most common musculoskeletal complaint in primary care shows that clinicians must have an arsenal of quality interventions to treat this problem. The need for quality research and evidenced based guidelines are necessary to educate clinicians on their treatment options, the efficacy of those treatments, and their safety profiles.

Research Questions

1. In patients with shoulder pain, is oral non-steroidal anti-inflammatories or corticosteroid injections into the glenohumeral joint more effective in reducing shoulder pain?
2. What are the risks and side effects of oral non-steroidal anti-inflammatories and corticosteroid injections into the glenohumeral joint when used to treat shoulder pain?

Methodology

My search strategy consisted of searching the PubMed and Cochrane database for relevant articles. Article types included randomized controlled studies, systematic reviews, meta-analysis, and observational studies. Keywords used in PubMed were shoulder pain, NSAID, steroid injection, non-steroidal anti-inflammatories, corticosteroid injections, side effects, and adverse reactions. Keywords used in the Cochrane database were NSAIDs and shoulder pain. The systematic review found with those search parameters in the Cochrane database included corticosteroid injections thus no further keywords were used. Along with the database search, articles were gathered using the “similar articles” section within PubMed, as well as bibliography reviews on large systematic reviews as they pertained to my specific research question. Articles that did not compare oral NSAIDs and corticosteroid injections and that only examined one treatment approach were excluded. There were no exclusion criteria for older articles, patient age, or type of condition due to limited number of studies on this topic. A total of nine articles were found that address my first research question. There were numerous studies that examined side effects of oral NSAIDs thus large systematic reviews with a large number of participants were used to address my second research question.

Literature Review

This review will be broken down into two themes with each theme addressing one of my research questions. Theme one being the efficacy of oral NSAIDs compared to corticosteroid injection which will address my first research question. Theme two being adverse reactions of oral NSAIDs and corticosteroid injections which will address my second research question. Information was limited in theme one as this review seeks to examine the direct comparison of these two treatments to each other and not the efficacy of one treatment alone. Thus, older studies had to be included for theme one due to the scarcity of research.

Pathophysiology

The glenohumeral joint is a ball and socket joint with six degrees of freedom. It is formed by the convex surface of the humeral head and the glenoid of the scapula. The glenoid has a cartilaginous rim around it that functions to increase the surface area of the joint and to deepen the glenoid thus providing increased stability. The joint is then surrounded by a joint capsule made up of dense connective tissue to further increase stability. The joint capsule is then further broken down into glenohumeral ligaments. The joint capsule is surrounded by tendons of the rotator cuff which provide dynamic stability throughout motion. There are bursas which lie under certain tendons to reduce friction. These structures are then surrounded by muscle and tendons from larger muscles that function to move the joint throughout its entire range of motion (Drake, Vogl, & Mitchell, 2015).

The shoulder joint's ability to move throughout a larger range of motion than other joints comes with the possibility of having multiple different structures that can be injured thus creating shoulder pain. Injuries can range from fracture, cartilage tears, tendonitis/osis and

tendon rupture, bursitis, capsulitis, and capsular tears to non-traumatic injuries like osteoarthritis. The literature review focuses on shoulder pain only and does not break down the efficacy of these treatment modalities to one type of shoulder condition.

Theme 1- Efficacy of Oral NSAIDs Compared to Corticosteroid Injection

Adebajo, Nash, and Hazleman, (1990) conducted a prospective double-blind placebo controlled study that was designed to determine if oral non-steroidal anti-inflammatories (NSAIDs) and local corticosteroid injections are superior to placebo in patients with shoulder pain. There were three groups in this study with 20 participants in each group. Patients who had shoulder pain for less than three months were included in this study. Group one received oral diclofenac (NSAID) as well as a sub-acromial injection of lignocaine. Group two received oral NSAID placebo tablet and an injection of lignocaine, as well as triamcinolone hexacetonide. Group three received oral NSAID tablets and an injection of lignocaine. Each group was given instructions on home physical therapy exercises and told to perform the same exercise regimen post treatment at home. They found both oral NSAIDs ($p=0.0268$) and triamcinolone injection are superior to placebo with the steroid injection group achieving the greatest results. Although there was improvement there was no statistical significance. However, they did find that in those defined as responders (improvements in all three variables) versus non-responders that there was statistical significance ($p=0.0269$) with steroid injection being superior to oral NSAIDs. Thus, the steroid injection is more likely to improve all three variables (function, range of motion, pain) than oral NSAIDs alone. The final recommendation was initial treatment with oral NSAIDs and physical therapy. If there was no improvement in two weeks then local corticosteroid should be administered.

This study appears to have several limitations that were not addressed within the article. Their research question was not clearly stated and lacked a specific hypothesis. They also allowed patients that had previously been on oral NSAIDs into the study. Although they had them stop taking the oral NSAIDs seven days prior to entry into the study, they did not address which or how many patients were on NSAIDs in their discussion. They measured three outcomes in the study: pain, functional limitation, and range of motion. Functional limitation was measured using a numerical grading system (0-3) with associated none, mild, moderate, and severe. There was no mention of how they defined functional limitation or if they used an evidence based functional outcome measure. This could bias results as a participant's perception of the same limitation maybe different.

Berry, Fernandes, Bloom, Clark, and Hamilton (1980) conducted a single-blind study comparing the efficacy of acupuncture with steroid injections, physiotherapy, and or NSAIDs. It was a small study with 60 participants with intentions of being a pilot study due to the small number of participants. There were five groups: acupuncture, steroid injection plus placebo NSAID, steroid injection plus active NSAID, physiotherapy in the form of ultrasound, and placebo NSAID and ultrasound with 12 participants in each group. Patients were included that had a doctor's referral for a "cuff lesion." Patients with painful arc syndrome and "frozen shoulder" syndrome were excluded. The steroid medication that was used was 40 mg of methylprednisolone with two ml of 2% lignocaine. Tablets of 200 mg tablets of tolmetin sodium dosed two tablets three times daily was used for the oral NSAID group. All groups showed statistically significant improvement in pain and range of motion but no significant difference between groups with no distinct advantage of any treatment.

There were some limitations to this study in that some of their data was difficult to interpret. It was not clearly outlined in the article how they developed their data and the tables within were not easy to interpret. One outcome measure, success or failure, was measured as a subjective opinion by an assessor of unknown qualifications. Despite showing statistical significant improvement in pain and range of motion, the placebo physiotherapy and NSAID group was the only one labeled as having higher than a 50% success rate. There was no mention of why this may have occurred. They also only followed patients through four weeks where other studies followed patients out as far as 6 months.

A randomized clinical trial conducted by Dehghan et al. (2013) compared the efficacy of glenohumeral injections of corticosteroids to oral NSAIDs in diabetic patients with frozen shoulder. It began with 75 total participants and lost 18 because of failure to follow up resulting in a total of 57 patients. They had a detailed list of exclusion criteria including, but not limited to, pain greater than 6 months, infection, fractures, stroke, GI disorder, and kidney injury. Group one consisted of oral NSAIDs (naproxen) while group two received an intra-articular corticosteroid injection (triamcinolone) with ultrasound guidance. Patients were seen five times post treatment for assessment and followed for a six-month period. They found a significant improvement in pain ($p=0.91$) and range of motion (flexion $p=0.51$, abduction $p=0.76$, external rotation $p=0.12$, internal rotation $p=0.91$) in both groups but found no statistical difference between the two treatment groups. Their final recommendation was to start with corticosteroid injection due to the possible side effects of NSAIDs in diabetics with multiple comorbidities. There were some limitations however, in that it only compared these treatment modalities to diabetics with frozen shoulder where my research question pertains to a broader diagnosis of shoulder pain.

According to Karthikeyan et al. (2010) there is a statistically significant improvement in outcomes when comparing corticosteroid injection to NSAIDs in patients with subacromial impingement. They conducted a double-blind randomized controlled trial that looked at comparing the efficacy of shoulder injections of an NSAID and a corticosteroid in improving pain and function in patients with subacromial impingement. Patients above 18 years of age that had a diagnosis of subacromial impingement were included. Patients were excluded if they recently had a shoulder injection, currently taking regular NSAIDs or steroids, other shoulder pathology, pregnant or breast feeding, or in litigation regarding their shoulder condition. There were 58 patients in this study, with two lost to follow up, and were each randomly selected to be in one of two groups. Group one received a single injection of tenoxicam 20 mg (NSAID) and Group two received a single injection of methylprednisolone 40 mg (corticosteroid). Three functional outcomes measures were used to assess improvement including the Constant-Murley Shoulder score, the Disability of Arm, Shoulder, and Hand score, as well as the Oxford Shoulder score. The use of these evidenced based objective outcome measures improves the strength of this study as the validity of these tools have already been established. Improvements in the Constant-Murley score were found in both groups with the steroid group being statistically significant ($p=0.0030$). In terms of subjective assessment, they found no statistical significance in shoulder function between the two groups ($p=0.091$). They found that the patients in the steroid group showed statistically significant improvement in objective outcome measures at six weeks compared to the NSAID group.

This study differed slightly compared to the others as it looked at an injection of NSAID into the shoulder as opposed to oral medications. I included this due to the limited studies on oral drugs and that one might extrapolate this research to some degree to assist in answering my

research question. It has some limitations however, in that it only follows patients for six weeks, as subacromial impingement is a chronic problem. It leaves room for further clinical questions regarding long term efficacy and other modalities to study along with this protocol.

Petri, Dobrow, Neiman, Whiting-O'keefe, and Seaman (1987) conducted a double-blind, placebo-controlled study whose goal was to investigate the therapeutic effect of oral nonsteroidal anti-inflammatories (NSAIDs) and a local injection of corticosteroid alone and in combination. There were 100 participants in this study that met at least 2 of 3 of these criteria: painful abduction, painful arc of movement from 45 degrees to 120 degrees, or supraspinatus insertion tenderness. There were four groups in this study with 25 in each group. Group one was given 4 cc of 1% lidocaine injection and 500 mg of naproxen dosed at twice daily for 30 days. Group two was given 3 cc of 1% lidocaine, 500 mg of naproxen dosed at twice daily for 30 days, and 1 cc of 40 mg/ml of triamcinolone. Group three was given 3 cc of 1% lidocaine, 1 cc of 40 mg/ml of triamcinolone, plus a placebo pill twice daily for 30 days. Group four was given 4 cc of 1% lidocaine plus placebo pill twice daily for 30 days. They measured active abduction, pain, and the patient's determination of limitation of function. These variables were individually compared as well as combined with equal weight into a "clinical index". The higher the clinical index the better the outcome. They found that steroid injection ($p=0.00005$) and oral NSAIDs ($p=0.02$) were statistically superior to placebo and that there was no statistical significance of combined treatment compared to steroid injection alone. Steroid injection alone is superior to oral NSAIDs alone but only in terms of pain ($p=0.04$) and their "clinical index" ($p=0.04$) but not in active motion and limitation of function. Overall, this was a well-designed study with good methods and data analysis with no mention of limitations by authors.

Ranalletta et al. (2016) conducted a randomized single-blind controlled trial in order to determine that in patients with adhesive capsulitis, a single intra-articular corticosteroid injection given before the beginning of a therapy program resulted in faster pain relief and recovery of function compared with oral NSAIDs. There was a total of 74 patients that were separated into two treatment groups. Group one was the intervention group and received an intra-articular injection of corticosteroid. Group two was the control group and received diclofenac 75 mg (NSAID) two times per day. Patients followed up at two, four, six, eight, and 12 weeks and pain was assessed using the visual analog scale (VAS) and passive range of motion (PROM) was measured using goniometry. Secondary outcome measures included the American Shoulder and Elbow Surgeons Shoulder Score (ASES), QuickDASH, and Constant-Murley score.

Ranalletta et al. found that pain was improved at all time points regardless of treatment group. However, relief was achieved faster in the corticosteroid injection group. This was statistically significant up to eight weeks ($p < .001$), but lost significance ($p = .825$) at 12 weeks as pain improved in the oral NSAID group. Statistically significant differences were found in all functional outcome measures at the early time points. The ASES showed significant improvement early on but lost significance at 12 weeks ($p = .167$). The Constant-Murley score maintained significance ($p = .010$ at 12 weeks) throughout the study and the Quick Dash lost significance after week 8 ($p = .461$ at 8 weeks). PROM measurements showed significant improvement in the corticosteroid group up to the end of the study. There were no serious complications in either treatment group. Two patients did have facial flushing that resolved spontaneously in the injection group. Overall, they found that a single intra-articular corticosteroid injection accelerated pain relief and functional improvement in patients with adhesive capsulitis. The main limitation to this study was a relatively short follow up. Although

Ranalleta et al. only followed patients through 12 weeks, they did assess patients at multiple intervals along the way.

Shin and Lee (2013) conducted a randomized controlled trial which aimed to determine the efficacy of a single corticosteroid injection delivered at different sites and compare it to outcomes achieved with oral NSAIDs in patients with adhesive capsulitis. There were 191 participants that were randomly assigned to four treatment groups (three corticosteroid injection groups and one oral medication group) and compared outcomes for pain and mobility. The corticosteroid injection groups one through three received 4 mL of 2% lidocaine and 40 mg of triamcinolone (1mL) and group four received oral diclofenac 100 mg twice daily for 6 weeks. They measured pain using the VAS, active range of motion (AROM) using goniometry, and function with the shoulder questionnaire ASES. All patients underwent a home exercise program and performed the same exercises. They found that all patients treated with corticosteroids, regardless of group, demonstrated statistically significant ($p < .05$) faster pain relief and functional recovery up to 16 weeks compared to oral NSAIDs. Although corticosteroids were found to achieve faster results, at 24 weeks there was no statistical difference ($p = .670$) in outcomes for all four groups. Shoulder motion and functional outcomes improved in all groups with the faster recovery in the injection groups. However, at 24 weeks there were no significant differences between the four groups ($p = .117$). There were no serious side effects in the injection group. Three patients had temporary skin color changes and seven developed a steroid flare reaction.

There were some areas that could have been refined to improve the strength of the study. One requirement for inclusion was older than 18 years old. A condition like adhesive capsulitis generally affects older individuals and subjects that young will heal faster. Thus, narrowing the

age range down to an older population would mean this data could be extrapolated to that population you would normally see in the clinic. There was also a standardized home exercise program initiated at 4 months post treatment but there was no mention of how they measured compliance to this protocol once the patients returned home. The small sample size also makes it difficult to compare to the general population. The strength of this study lies in the design of the four groups and how they delivered the medication at multiple sites and routes.

White, Paull, and Fleming (1986) conducted a double-blind, double-dummy protocol that compared the efficacy of injections of long acting corticosteroids to indomethacin (NSAID) in patients with acute rotator cuff tendonitis. There were two groups in this study with a total 40 participants, five in each group were lost to follow up. Group one consisted of capsules of 25 mg of indomethacin and 1 cc saline injections as placebo. Group two consisted of placebo capsules and injection of 1 ml of 40 mg/ml triamcinolone. Patients were then reassessed three weeks after initial treatment and pain and range of motion were measured. It was found that both groups showed improvement in motion and pain variables but there was no difference in short term response between the two treatments. It was recommended that NSAIDs should be used for initial therapy with corticosteroid injections reserved for those who did not respond to NSAIDs.

White et al. conducted a well-designed study but it had some limitations. First, this study had a small sample size of 40 participants with 10 that were lost to follow up. Secondly, one of the authors was an examiner and participated in evaluating patients for inclusion into the study creating an opportunity for bias. Lastly, their system for measuring improvement was complex and included more than one subjective criteria that was determined by the examining physician. It did not mention whether the physician was one of the authors but it is possible and should have

been stated. The subjectivity of the physician's assessment of improvement could also have affected the difference in findings compared to the other studies.

Sun, Chen, Li, Jiang, and Chen (2015) conducted a systematic review comparing steroid injections and NSAIDs. There are previously two other meta-analyses comparing these but they were older and did not include any of the newer studies, thus they were excluded. Through literature review they identified eight studies for their comparison which is more than the previous two meta-analysis on this subject. Five studies compared steroid injection to oral NSAIDs and three studies compared steroid injection to NSAID injection. There were differing diagnoses of shoulder pain in each study which included adhesive capsulitis, tendonitis, impingement syndrome, and unspecified pain. They found that in terms of functional improvement, steroid injections showed superiority to oral NSAIDs (standard mean difference (SMD) 0.61; 95%CI, 0.08–1.14, $p=0.01$) and found no superiority in either treatment in pooled results in regard to pain relief (SMD 0.45; 95%CI, 0.50–1.40, $p<0.00001$). They also examined complications associated with each treatment. In pooled results, they found no superiority in favor of either treatment indicating equal safety for both treatments (relative risk (RR) 1.10; 95% CI, 0.26–4.58, $p=0.29$). Some commonly reported complications were skin color change and facial flushing from the injection. There were two gastrointestinal reactions, one headache, and two with dyspepsia found. Overall, steroid injections are more effective than oral NSAIDs in improving shoulder function but both treatments show equal efficacy in treating shoulder pain. Both steroid injection and oral NSAIDs are safe in treating shoulder pain but there are still risks in patients with pre-existing conditions who take oral NSAIDs and this should be considered in determining treatment approach.

There are some limitations to this review mentioned by Sun et al. in their discussion. First, the data could be less reliable due to failing to include all diseases that can lead to shoulder pain. There was also a lack of consistency in detailed intervention protocols across some the studies they examined which may have an influence on the overall outcomes. Lastly, Sun et al. mentioned that, “some estimated data were input into comparison and some data were lost, which could exert and influence on pooled results” (Sun et al., 2015, p. 7).

Theme 2- Adverse Reactions of Oral NSAIDs and Corticosteroid Injections

Chang et al. (2011) conducted a case-crossover design that looked to assess the relationship between NSAID use and the risk of hospitalization for upper GI events. They analyzed information from the Taiwan National Health Insurance Database and identified all patients >20 years old that were hospitalized for upper gastrointestinal events. They found 40,635 patients that met the inclusion criteria. They examined the use of selective, non-selective, and parental NSAID and its effect on upper GI complications. They found that all NSAIDs are associated with higher risk of upper GI toxicity compared to non-use but showed variability among individual NSAIDs and routes. The adjusted odds ratio (OR) for celecoxib (selective NSAID) was 1.52 (95%CI: 1.27-1.82) and for oral non-selective NSAIDs was 2.56 (95%CI: 2.44-2.69). The highest risk of complications was parental use of ketorolac with OR of 5.76 (95%CI: 5.14-6.44). They determined that Celecoxib, ibuprofen, and mefenamic acid had lower risk than other NSAIDs and that parental delivery substantially increased risk compared to oral administration. Chang et al. only studied the Asian population and there may be aspects of the diet, customs, and culture that may make them more or less prone to adverse events.

Dean et al. (2014) conducted a systematic review that examined the effects of glucocorticoid injections on tendon tissue and tendon cells and looked to summarize the

histological, molecular, and mechanical changes. It identified 4,424 studies with 50 articles being used in the review after not meeting inclusion criteria. They found multiple different effects on the tendon tissue following a glucocorticoid injection. In six studies, there was decreased collagen organization and an increase in collagen necrosis in three studies. Fibroblast proliferation was reduced in eight studies and there was decreased viability in nine studies. An increase in inflammatory cell infiltrate was shown in four studies and an increase in cellular toxicity was found in four studies. Collagen synthesis was decreased in 17 studies. There was an increased ratio of type III collagen compared to type I in three studies. There were 18 studies that examined the mechanical properties of the tendon. Six showed a decrease, three showed an increase, and nine showed no change.

Overall, Dean et al. found that local glucocorticoids have negative effects on tendons in vitro as well as increased collagen disorganization and necrosis in vivo. There are short term reductions in mechanical properties of the tendon post-injection. Data was gathered and a forest plot was made showing the overall effect size was -0.67 (95%CI: -0.01 to -1.33, $p=0.046$) showing a trend towards a reduction in mechanical properties of the tendon after injection. They concluded that the risks for injecting tendons with glucocorticoids are present and the decision to use them should be made on an individual basis as the evidence points to negative histological and mechanical changes. The authors of this study designed a good set of inclusion/exclusion criteria which helped eliminate poor studies. They excluded studies without control groups and that did not assign a p-value or statistical significance to their data, which helped give strength to the data that they pooled from the studies. Some of the articles were animal studies which one could argue cannot be applied to human tissue.

García Rodríguez and Barreales Tolosa (2007) conducted a retrospective study cohort with a nested case control analysis. They used The Health Improvement Network (THIN) database in the United Kingdom between the years 2000 and 2005 for patients between 40 and 85 years of age, taking non-selective and selective NSAIDs and that had an adverse event or were hospitalized due to upper gastrointestinal complications (UGIC). They examined 1,561 cases of patients with UGIC after taking an oral NSAID. Among non-selective NSAIDs, they found that the relative risk (RR) of developing UGIC is 3.7 (95% CI: 3.1-4.3). There is an association with UGIC and dose with the relative risk at low-medium dose is 2.5 (95% CI: 2.0-3.2). The risk doubles in those who received high doses, 4.9 (95% CI: 4.0-6.1). They also found the non-selective NSAIDs with a plasma half-life of less than 12 hours reduced the risk of UGIC compared to long half-life drugs, RR 4.5 (95% CI: 3.3-6.2) compared to 2.4 (95% CI: 1.9-3.1). In selective NSAIDs at low-medium doses, the RR was 2.3 (95% CI: 1.5-3.5) and at high doses 3.1 (95% CI: 1.8-5.2). Overall, García Rodríguez and Barreales Tolosa concluded that the use of non-selective NSAIDs is associated with a three to four-fold increase in UGIC where the use of selective NSAIDs corresponds to a two to three-fold increase. Although, taking aspirin with a selective NSAIDs cancels out the superior safety profile of the selective NSAIDs, the risk of UGIC is also determined by the daily dose and half-life of a particular drug.

The authors did mention specific limitations and their attempts to correct for these using statistical methods. These limitations were mostly in the data collection as this was a retrospective design. There was a possibility of confounding but they controlled for “risk factors and defined treatment” (García Rodríguez and Barreales Tolosa, 2007, p. 505) which decreased this effect. Secondly, was the inability to monitor over-the-counter drug use as they used computerized prescription data for the analysis. Lastly, their primary source of data was

gathered using computerized prescriptions records in that in some instances did not end up in pharmacy filling. Thus, García Rodríguez and Barreales Tolosa stated that “this limitation applies rather exclusively to acute prescription use and would tend to slightly underestimate the risk among short-term users” (p. 505).

Habib, Saliba, and Nashashibi (2010) looked to review all the published English literature regarding local effects of intra-articular corticosteroid injections (IACI) in humans up to the year 2008. They found there were multiple local side effects ranging from mild to serious in severity. It was shown that there was a low rate of joint infection post injection (1:1,000-1:25,000) and that the prognosis of joint infection was not different than those who had not received an IACI. The most common local effect was calcifications (4% intra-articular, 50% peri-articular) in the joint capsule following injection that were mostly asymptomatic unless they affected the mechanical properties of the joint. Skin atrophy and depigmentation (5%) were non-serious side effects noted but were less common in large joints due to increased accuracy of injection in those joints. Charcot arthropathy and Nicolau’s syndrome had been reported but were extremely rare. Acute synovitis was a rare reaction but was usually caused by the delivery of short-acting agents. Avascular necrosis was found in women with IACI of the hip with unilateral osteoarthritis. Tendinopathy including tendonitis or rupture was most common in the Achilles and biceps tendon following a single IACI, but was reported as a rare complication.

Habib et al. did not mention specifics regarding their data or how they analyzed the results. It is unclear if one could extrapolate those percentages in clinical decision making or in educating patients about possible side effects. On review of their bibliography, there were 64 studies listed, but again no mention in the review itself of how they were analyzed.

Chou et al. (2016) conducted a nested case-control population based study that looked to evaluate time-dependent association of NSAID (selective and non-selective) with acute kidney injury (AKI). The authors analyzed the Taiwanese National Health Insurance Database and found 6,199 patients with AKI that matched the inclusion criteria for this study. They searched for patients who were admitted with the main diagnosis of AKI. They grouped patients into three groups: current users, recent users, and past users. They defined current users as those who were diagnosed with AKI within their prescription period. They defined recent users as those diagnosed with AKI 1-30 days after the termination of the prescription period. They defined past users as those who were diagnosed with AKI 31-180 days after prescription termination period.

Chou et al. found that the risk of hospitalization for AKI was highest among current users (OR 2.73, 95%CI: 2.28-2.38, $p < 0.001$) compared to recent users (OR 1.17, 95%CI: 1.01-1.35 $p = 0.035$). The use of non-selective NSAIDs for current users (OR 2.76, 95%CI: 2.31-3.30, $p < 0.001$) compared to selective NSAIDs for current users (OR 0.98, 95%CI: 0.66-1.46) was associated with increased risk of hospitalization for AKI within one month of first prescription for current non-selective NSAID users. Specifically, the risk for AKI was insignificant for celecoxib OR 1.07 (95% CI 0.67–1.72) and etoricoxib OR .39 (95%CI: 0.15-1.05).

There were some limitations in this study due to its retrospective observational design. The main limitation was the risk for confounding, but Chou et al. attempted to adjust several covariates that may influence AKI risk to reduce this effect. Secondly, there may have been bias between 2 cohorts but they believed this to be negligible due to the large sample size. Lastly, there were several confounding factors that could not be adjusted for (vital signs, tobacco use, family history, nutrition, alcohol consumption, etc.) as this information was not listed in the computerized registry.

Patel and Bahna (2015) authored a review article that looked at English-language literature throughout an 11-year period (2004-2014) for reported immediate-type hypersensitivity reactions caused by corticosteroid administration. They found 48 articles addressing hypersensitivity reactions and found 120 reactions in 106 patients that occurred after systemic or topical administration of corticosteroids. They found the prevalence of hypersensitivity reactions to be relatively rare at 0.1% to 0.3% (Patel and Bahna, 2015, p. 178). The most common reaction was non-fatal anaphylaxis, found in 67 (63.2%) patients, with the intravenous (IV) route being the most common and intra-articular second most common. Methylprednisolone was most commonly implicated in anaphylaxis followed by triamcinolone acetate. Urticaria and angioedema was the second most common reaction, found 32 times in 29 (27.4%) patients, with the oral being the most common route. They found that bronchospasm and dyspnea were only present in six patients. All six were caused by administration of IV corticosteroids. It was mentioned that this reaction may be under reported as corticosteroids are generally considered a rare reaction in patients with asthma. One of the reactions out of the six patients was caused by a hypersensitivity reaction to the inactive-ingredient succinate ester. A rash developed in eight times in six patients. They were unsure to the exact etiology of the rash as skin testing was only positive in four out of six patients. Immediate hypersensitivity reactions can occur through any route with IV being the most common followed by oral and then intra-articular.

The purpose of Patel and Bahna's article seemed geared toward education and informing so clinicians are aware that both minor and serious hypersensitivity reactions can occur from corticosteroid use. This review did not mention the details of their data analysis and just focused on the percentages of hypersensitivity reactions to all routes of administration.

Viala, Dougados, and Gossec (2009) performed a meta-analysis that looked at the efficacy and safety of steroid injections for shoulder and elbow tendonitis. They found 218 potential relevant articles and excluded 199 leaving 16 RCTs for efficacy and 19 for safety. This included a total of 1,731 patients with 744 (43%) that were treated by injection and 987 by controls. Pooled analysis showed short term effectiveness of steroids compared to pooled control for pain and function. At week 1-3 effect size (ES)=1.18 (95%CI:0.27-2.09), week 4-8 ES=1.30 (95%CI:0.55-2.04), week 12-24 ES=0.38 (95%CI:-0.85-0.08), and week 48 ES=0.07 (95%CI:-0.60-0.75). They found that steroid injections improved pain and function more than NSAIDs in the short term, up to eight weeks. Although pain and function improved in the short term, corticosteroid injections showed not to be superior or statistically significant when compared to NSAIDs. At long term follow up, they found that patients treated with steroid injection had no difference in pain and appeared to be less effective on functional disability than other pooled treatments. In regards to safety, in 1,754 patients they found that the main side effect was transient pain after injection followed by skin atrophy or depigmentation. There were no treatments discontinued due to toxicity and they determined the number needed to harm (NNH) was 26. There were no reported tendon ruptures in all 1,754 patients. Their overall findings after their review in terms of efficacy were that steroid injections are effective in acute or subacute tendonitis (<12 weeks) but they were not superior to NSAIDs. In regards to safety, they determined that steroid injections are well tolerated with rare and minor side effects.

There were a few limitations mentioned to this meta-analysis by Viala et al. There were few RCTs on the diagnosis and treatment on tendonitis and of those the outcomes used were heterogenous. Many of the studies examined used a qualitative evaluation design. Lastly, there was some risk of publication bias with this meta-analysis.

Nissen et al. (2016) conducted a randomized, multicenter, double-blind, noninferiority trial to investigate the cardiovascular risk of celecoxib, naproxen, and ibuprofen otherwise known as PRECISION. Patients were selected that had known cardiovascular disease or an increased risk of developing cardiovascular disease. Patients were put into one of three groups and numbers ranged from 7,969-8,072 in each group. They found statistically significant results that there is no greater cardiovascular risk from celecoxib when compared to naproxen or ibuprofen. Also, it was noted that naproxen did not show better cardiovascular outcomes compared to other NSAIDs. They also included an arm that addressed gastrointestinal and renal related side effects. They found that with celecoxib, there were significantly fewer gastrointestinal events compared to ibuprofen and naproxen even with the addition of a proton-pump inhibitor. Hazard ratio (HR) for celecoxib vs. naproxen group were (0.71; 95% CI, 0.54 to 0.93; P=0.01) and for the celecoxib vs. ibuprofen group (HR 0.65; 95% CI, 0.50 to 0.85; P=0.002). They also discovered that there were fewer renal and hypertensive adverse events in the celecoxib compared to the ibuprofen group (HR 0.61; 95% CI, 0.44 to 0.85; P=0.004). No significant difference was found in the celecoxib and naproxen group (HR 0.79; 95% CI, 0.56 to 1.12; P=0.19).

The primary limitations to this trial mention by Nissen et al. were adherence and retention which was consistent among all treatment groups as well as the “possibility of informative censoring” (Nissen et al., 2016, p. 2528).

Castellsague et al. (2012) conducted a systematic review and meta-analysis of published observation studies and determined pooled relative risk (RR) of upper gastrointestinal complications (UGIC) associated with NSAIDs. Initial search yielded 2,984 articles but only 28 met inclusion criteria and were included in the meta-analysis. They listed extensive and detailed

inclusion criteria for each of the 2,984 studies found accounting for the large number of excluded studies. They found the lowest RR for UGIC in aceclofenac 1.43 (95% CI: 0.65, 3.15), celecoxib 1.45 (95% CI: 1.17, 1.81), and ibuprofen 1.84 (95% CI: 1.54, 2.20), and intermediate RR between 2 and 4 for the remainder of NSAIDs studied. They also found a dose-dependent association with UGIC. High daily doses were shown to have a two to three-fold increase in RRs for UGIC while those taking low-medium doses, except celecoxib, did not have a dose-dependent relationship. Overall, for individual NSAID use, they determined that ibuprofen was in the lowest range of pooled RRs while naproxen was associated with higher RR values depending on certain doses. Primary limitations to this review was heterogeneity among the studies examined as well as confounding due to the use of observational studies.

Zhang, Donnan, Bell, and Guthrie (2017) performed a systematic review of high-quality population-based observational studies to determine the risk of acute kidney injury (AKI) due to NSAIDs in the general population in people with and without chronic kidney disease (CKD). The initial search yielded 4,629 records with an end total of 3,789 after duplicates were removed. The abstracts were reviewed for eligibility into the study and then the full text was retrieved for review if deemed appropriate. A total of 30 full text articles were included for eligibility. Those 30 were then subjected to an extensive list of exclusion criteria, and only 10 studies were selected for review which included a total of 1,609,163 participants. AKI is generally considered to be a rare adverse effect of NSAIDs so they used odds ratios and noted that it should approximate to relative risk. They found that taking NSAIDs was associated in a 1.5-fold increase in the odds of developing AKI in the general population in people with (OR 1.63, 95%CI: 1.22–2.19, $p=0.009$) and without CKD (OR 1.73 95%CI: 1.44–2.07, $p < 0.001$). In older individuals, there was 2-fold risk in developing AKI with no strong evidence linking higher

COX-2 selectivity to decreased AKI risk. They could not determine absolute risk as the studies they examined did not report each patient's baseline risk of AKI. Overall, they found a statistically significant increase risk of AKI from exposure to NSAIDs as well as similar risk among all sub-groups studied. They advocate that clinicians should work to reduce exposure in groups that are susceptible to AKI such as people with advanced age, CKD, or those taking other nephrotoxic drugs.

Given the extensive list of exclusion criteria and the subsequent small number of studies reviewed in this study, heterogeneity among the 10 studies examined was present. Although Zhang et al. did attempt to correct for this in their statistical analysis. Confounding was also present due to the inclusion of observational studies. Lastly, they only included articles published in English which limited to the amount of studies eligible for inclusion thus contributing to heterogeneity.

Patrono (2016) conducted a review with the goal of identifying cardiovascular risks associated with NSAID use and to discuss strategies to optimize therapy. They found that aspirin had dose dependent cardiovascular effects. At higher doses, it had an effect on increasing blood pressure, increased risk of heart failure, and a negative interaction with antihypertensive drugs especially angiotensin-converting enzyme (ACE) inhibitors. Patrono stated that "low dose aspirin does not affect renal function or blood pressure" (Patrono, 2016, p.) and has cardioprotective properties. Patrono (2016) determined that traditional NSAIDs and coxibs increased the risk of major vascular events by 40% with the exception of naproxen. Specifically, diclofenac (RR 1.70, 95% CI 1.19-2.41, p=0.0032), ibuprofen (RR 2.22, 95% CI 1.10-4.48, p=0.0253), and naproxen (RR 1.08, 95% CI 0.48-2.47, p=80). Even at high doses, naproxen did not show any statistically significant increase in risk for vascular or coronary events. He found

no evidence that there was an increase in risk of stroke in any NSAID and the risk of hospitalization from heart failure was doubled in all traditional NSAID (diclofenac RR 1.85, 1.17–2.94, $p = 0.0088$; ibuprofen RR 2.49, 1.19–5.20, $p = 0.0155$; naproxen RR 1.87, 1.10–3.16, $p = 0.0197$) as well as coxibs. Lastly, he determined the risk of vascular death was increased with significance in coxibs and diclofenac (RR 1.65, 95% CI 0.95-2.85, $p=0.0187$), increased without significance by ibuprofen (RR 1.90, 95% CI 0.56-6.41, $p=0.17$), and not increased by naproxen (RR 1.08, 95% CI 0.48-2.47, $p=0.80$). Patrono failed to list the specific data regarding the coxibs that he studied and only include the data for the traditional NSAIDs mentioned above.

Rostom et al. (2011) conducted a systematic review to determine gastrointestinal safety of cyclooxygenase-2 inhibitors (COX-2) compared to nonselective NSAIDs and with placebo. Their search returned 1,169 studies of which 69 met inclusion criteria. This review found a clear advantage of selective COX-2s over nonselective NSAIDs on gastrointestinal safety with fewer gastroduodenal ulcers (RR 0.26, 95%CI: 0.23-0.30) and fewer complications from ulcers (RR 0.39, 95%CI: 0.31-0.50). Rostom et al. mentioned that there is emerging data on the cardiovascular safety of these drugs and that clinicians need to be mindful of patients with cardiovascular disease and those with risk factors as more research is being done in regards to cardiovascular safety.

Discussion

With shoulder pain being as prevalent as it is and with the amount of primary care visits that occur due to shoulder pain, there must be good evidenced based treatments that primary care providers can employ to effectively treat these patients. Many primary care providers use one or both corticosteroid injections and oral NSAIDs in the management of patients with this problem. In conducting this review, there were few studies that specifically compared corticosteroid

injections in the shoulder to oral NSAIDs for treating shoulder pain. The majority of evidence examined each treatment approach alone in treating pain and did not examine whether one was superior to the other. I reviewed a total of nine studies to determine an answer to my theme one question. One study being a systematic review and one other study, Karthikeyan et al. (2010), that compared corticosteroid injection to NSAID injection and not an oral NSAID. I included it in my review only because of the shortage of studies on this topic with hopes of extrapolating the data and comparing their results to the other studies. Therefore, its results should be interpreted with caution.

In patients with shoulder pain, is oral non-steroidal anti-inflammatories or corticosteroid injections into the glenohumeral joint more effective in reducing shoulder pain?

Many of the studies comparing corticosteroids to oral NSAIDs yielded similar results (Berry et al., 1980; Deghan et al., 2013; Petri et al., 1987; Ranelleta et al., 2016; Sun et al., 2015). Two studies found that corticosteroids and oral NSAIDs are both superior to placebo in treating shoulder pain (Adebajo et al., 1990; Petri et al., 1987). Three studies found with statistical significance, that corticosteroids accelerate pain relief when compared to oral NSAIDs but long-term pain relief was equivocal (Dehghan et al., 2013; Ranelleta et al., 2016; Shin & Lee, 2013). Overall, both corticosteroid injection and oral NSAIDs are effective at reducing shoulder pain but there is no significant difference between the two treatments and one is not superior to the other.

What are the risks and side effects of oral non-steroidal anti-inflammatories and corticosteroid injections into the glenohumeral joint when used to treat shoulder pain?

In contrast to the general lack of evidence found in theme one, there is an abundance of literature on the safety of corticosteroid and oral NSAIDs. However, the literature has predominately examined one treatment approach or the other as there were no specific studies where the main goal was to assess side effects of corticosteroids versus oral NSAIDs. There are some studies in theme one that mentioned adverse effects and they reported uniform results in that there were no serious side effects (Adebajo et al., 1990; Karthikeyan et al., 2010; Ranelleta et al., 2016; Shin & Lee, 2013; Sun et al., 2015). This information must be interpreted with caution as this was not the goal of these studies but merely a mention within their discussion.

According to the literature reviewed, there is a risk for upper gastrointestinal complications (Castellsague et al., 2012; Chang et al., 2011; Garcia Rodriquez & Barreales Tolosa, 2007; Rostom et al., 2011; Nissen et al., 2016). Non-selective oral NSAIDs pose the greatest risk followed by selective oral NSAIDs. Although selective oral NSAIDs were found to decrease the risk of upper gastrointestinal complications, they found that taking aspirin with selective NSAIDs virtually cancels out their gastroprotective effect (Garcia Rodriquez & Barreales Tolosa, 2007). Many patients are on low dose aspirin for cardiovascular protection and this is something that needs to be considered when prescribing these agents. The studies showed an increase in cardiovascular risk to a varying degree of all NSAIDs (Chang et al., 2011; Nissen et al., 2016; Patrono, 2016). This includes an effect on blood pressure, increased risk of hospitalization due to heart failure, and their effects on the kidney. It was demonstrated that all NSAIDs pose a risk to the kidney and AKI is possible in healthy populations as well as the elderly (Chou et al., 2016; Zhang et al., 2017). There were some hypersensitivity reactions

associated with corticosteroids including non-fatal anaphylaxis, urticaria, angioedema, rash, skin atrophy, and skin depigmentation (Patel & Bahna, 2015).

Several limitations need to be addressed when examining the literature for theme one. First, there are relatively few studies directly comparing corticosteroids to oral NSAIDs and its effect on shoulder pain. There are many that look at shoulder injections and oral NSAIDs alone and did not meet the inclusion criteria, but few that directly compare the two treatments and address which is superior. Second, all the studies in theme one had small sample sizes and relatively short term follow up. These small sample sizes make it difficult to extrapolate the results of this review to the general population. Third, these studies lacked consistency on treating the same shoulder condition. There are numerous causes of shoulder pain and many structures within the shoulder that can be involved that generate pain. There were few studies that compared these two treatments with the same shoulder condition and patients with the same demographics and comorbidities. Although there was a lack of consistency in pathology in these studies, the results were mostly consistent among all the studies showing that both treatments are effective against a wide range of conditions that cause shoulder pain. Lastly, some of the studies in theme one are very antiquated and were only included due to the general low number of studies on this topic. Thus, the overall findings of these studies for theme one need to be interpreted with caution. There were several current studies for theme two which is why newer large systematic reviews were included in the review. None of these limitations existed for theme two due to the high number of quality studies and reviews with very large sample sizes.

Application to Primary Care

In conclusion, there seems to be some evidence that corticosteroid injection accelerates pain relief in patients with shoulder pain but no treatment was superior to the other at long term

follow up. Both corticosteroid injections and oral NSAIDs proved to be superior to placebo in treating shoulder pain. There are side effects associated with both treatments. Oral NSAIDs appear to have more serious side effects including upper gastrointestinal damage, kidney damage, and increased cardiovascular risk while corticosteroid administration demonstrated mostly local side effects. Systemic side effects can occur but proved to be very rare.

Current clinical practice and administration of these modalities seems to be guided by clinician preference, practice setting, and experience with shoulder injections. The results of this review are applicable to clinical practice in that it can guide a clinician on what treatment to use depending on a patient's unique circumstances. For those clinicians that do not feel comfortable with performing shoulder injections, the evidence shows that they can achieve equal efficacy by treating with oral NSAIDs. These results also give clinicians a valuable educational tool when patients are inquiring about treatment options for painful shoulder conditions. The literature does show that both corticosteroid injections and oral NSAIDs are superior to placebo in treating shoulder pain and that there are evidenced based options for providers in managing shoulder pain. Although these treatment approaches prove to be effective, they still should be used cautiously in patients with certain conditions, as one treatment approach may be more favorable based off the side effect profile and the patient's co-morbid conditions.

Overall, the decision on which treatment to use should be determined by each patient's presentation, risk factors, co-morbidities, expectations, and goals for treatment. There does seem to be a place for both of these treatment modalities in primary care but the decision on which should be determined by the aforementioned items. There are other options for patients with shoulder pain, such as physical therapy, which was not examined in this review. Future studies would need to incorporate a structured physical therapy program with a licensed physical

therapist and assess this both alone and with corticosteroid injections and oral NSAIDs. This would give a clearer picture and a more comprehensive examination of available options for treating shoulder pain. Shoulder pain is prevalent in primary care thus more research needs to be done that compares treatment options as opposed to examining them alone. In the end, this review did shed light on an area in need of newer quality research.

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