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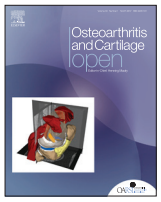

Clinical Trial

The most effective corticosteroid dose in the treatment of glenohumeral osteoarthritis: Feasibility pilot and protocol for double blinded randomized controlled trial

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ABSTRACT

Objective: Osteoarthritis affects over 5.4 million people in the United States. A common treatment is to perform intra-articular corticosteroid injections. However, the ideal steroid dose is unknown. This study aimed to pilot a corticosteroid injection protocol for primary glenohumeral OA.
Methods: We conducted a double blinded randomized feasibility pilot study. Patients with primary osteoarthritis of the glenohumeral joint were recruited and randomized to receive 20 mg, 40 mg, or 80 mg of triamcinolone. The primary outcome was the feasibility of the protocol and change in the Shoulder Pain and Disability Index (SPADI) 6 months following injection.
Results: 300 patients were screened for participation with 78 meeting inclusion criteria. 19 subjects completed the study. The most common reason for not participating was concern they would receive a smaller dose than previous injections. There was a 26% dropout rate, with 2 patients undergoing a total shoulder arthroplasty. There was no clinically significant difference ($p = 0.090$) between the groups at 6-months for the SPADI although all treatment groups showed a reduction of SPADI from baseline at 6 months. There was one adverse event in the 20 mg group, with a patient experiencing facial flushing after the injection.
Conclusion: We were successful in developing a feasible protocol. In the future excluding those who have received previous injections would be helpful for a higher enrollment rate. This patient concern highlights the need to complete clinical trials to guide medical decisions surrounding corticosteroid administration. NCT03586687.

1. Introduction

Osteoarthritis (OA) affects 54.4 million US adults and approximately half have arthritis-attributable activity limitation [1]. As the condition progresses, pain and functional disability increase. Patients usually begin treatment with conservative measures including physical therapy and administration of nonsteroidal anti-inflammatory drugs before obtaining a corticosteroid injection (CSI) [2]. CSI's have a patient-specific duration, often providing relief for a month before the effects begin to taper. Most individuals return to baseline by 2–3 months post injection [3,5].

Unfortunately, data on intraarticular injections is not robust and is primarily focused on hip and knee joint injections rather than the glenohumeral (GH) joint. There are minimal studies that directly compare differing steroid doses to each other and the data is mixed [6]. For example, steroid concentrations have been studied in adhesive capsulitis, where 20 mg and 40 mg of triamcinolone acetonide were used with no

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statistical significance between the two doses [7]. When a placebo was added, both doses were better than the placebo, but once again, no difference was seen between the two steroid concentrations [8]. In addition, a recent randomized controlled trial looked at 40 mg of triamcinolone vs 10 mg of triamcinolone in treatment of Adhesive Capsulitis. The authors concluded that the 2 steroid doses yielded similar improvements when measuring the Shoulder Pain and Disability Index (SPADI), visual analog score, and Range of motion [9]. Another study, looking at knee OA, found that high dose steroids had a larger effect on duration [4], but other studies have shown no difference in duration between the 40 mg and 80 mg concentration of triamcinolone acetonide [10].

Intraarticular injections do have adverse effects. Similar to systemic steroids, intraarticular injections have a similar side effect profile. Fortunately, intraarticular injections are localized, by nature of the procedure, and the chances of experiencing a significant side effect is rare [11,12]. The most common side effects are steroid flare, allergic reaction, facial erythema, hypopigmentation, fat pad necrosis, cutaneous atrophy, and a transient increase in blood glucose. Some of the rare side effects described in case reports include idiopathic central serous chorioretinopathy, decrease in breast milk production, sepsis, tendon rupture, and cataracts [12]. In addition, the minimum interval of intraarticular steroid administration is limited to three months due to a risk of tendon weakening and acceleration of cartilage loss [12,13].

There is a void of literature defining the ideal injectable steroid concentration in GH OA. Because of this, providers who perform intraarticular injections tend to rely on prior training experience or anecdotal evidence [14]. We aimed to evaluate the ideal steroid concentration to maximize treatment effects for GH OA, while minimizing the risk for side effects. To answer this question a protocol for a double-blinded randomized control trial was developed and the feasibility of this protocol was tested in anticipation of future studies. The primary outcome was feasibility of out pilot and change in overall SPADI after injection of 20 mg, 40 mg, or 80 mg of triamcinolone at 6 months post injection. We hypothesize that we will successfully pilot the feasibility protocol.

2. Methods

2.1. Study design

This protocol is a double blinded randomized controlled trial comparing 3 injectable corticosteroid concentrations and the change in overall SPADI scoring 6 months following injection. The protocol was approved by the Institutional Review Board as well as registered with clinicaltrials.gov prior to enrollment. Participants were identified from an outpatient clinic of patients scheduled for an ultrasound guided GH injection as part of their normal care after referral. The provider's schedules were reviewed and qualifying patients were identified. The patient was then contacted and the inclusion/exclusion criteria were reviewed with to assess patient eligibility. Inclusion criteria included radiographs with evidence of OA, 18 years of age or older, and clinical diagnosis established due to symptoms, including pain attributed to GH OA, pain with range of motion, and/or functional limitations longer than 3 months. Exclusion criteria included previous steroid injection into the GH joint in the previous 3 months, previous diagnosis of inflammatory arthritis, rotator cuff tear, immune compromise, previous shoulder surgery, allergy to steroid or lidocaine, a Kellgren-Lawrence classification of 1 or less on radiograph, non-English speaking, and inability to provide informed consent. Written consent was obtained at the time of the previously scheduled injection appointment for those eligible.

2.2. Intervention

At the time of consent patients were randomized by the research coordinator who choose blindly from an envelope into groups to receive GH CSI's consisting of 20 mg, 40 mg, or 80 mg of triamcinolone. The SPADI was also administered at the time of consent. The injection with the randomized steroid concentration was then drawn up with a mixture of 3 cc 1% lidocaine. The syringe was "blinded" by placing surgical tape over the syringe as to obscure the visual total volume of the solution. This would essentially blind the physician and the participant from the volume (and steroid dose) of the solution that was being injected. The patients then underwent a GH injection under ultrasound guidance. The physicians providing the injections have done over 800 GH injections and perform the injection with the same methodology, following the posterior approach in the lateral recumbent position. The patients were contacted at 2 weeks to evaluate for adverse outcomes. The patients were then contacted at 2 months, 4 months, 6 months, and 1 year for a SPADI assessment.

2.3. Statistical methods

The primary endpoint was change in overall pain score on the SPADI at six months from baseline. The sample size was determined based on assuming a minimal clinically meaningful difference in the 20 mg vs 80 mg groups as well as conducting non-inferiority tests in the 20 mg vs 40 mg and 40 mg vs 80 mg groups. For the first part, in the 20 mg vs 80 mg groups, we sought to have sufficient statistical power based on the assumption of a moderate Cohen effect size of 0.5. This required a sample size of 51 per group based on a two-sided 80%-power 5%-level *t*-test. For the non-inferiority test we allowed for a non-inferiority margin of 15 (so that differences of less than 15 were deemed clinically non-inferior), a sample size of 52 per group based on an 80%-power 2.5%-level (since there are two tests) non-inferiority test. Allowing for 10% loss to follow-up yielded a final sample size calculation of 57 per group for each of the three groups.

The primary endpoint was the change from baseline of the SPADI. The low dose and high dose changes were analyzed with a two-sided two-sample *t*-test. Noninferiority tests with a margin of 0.5 were used to test for a clinically meaningful difference between 20 mg and 40 mg doses and the 40 mg and 80 mg doses. The three groups were summarized with descriptive statistics and univariate statistical tests using analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and the Fisher's exact test for categorical variables. The demographic data and SPADI data were analyzed accordingly. All statistical analyses, graphics, and reports were prepared following best practices in conducing reproducible research in statistics utilizing various software packages built around the software platform.

3. Results

Patients were recruited over 3 years, starting in 2018. 300 patients were screened and 78 were found to meet all inclusion criteria. Of those that met inclusion criteria 31 declined participation, 11 were unable to be reached by phone, 5 were unable to be met in clinic, and 12 were lost for other reasons. Ultimately 19 completed the study. The overall recruitment rate for the study was 24%. There was a high rate of refusal at 40%. One of the common reasons for refusal to participate was apprehension of receiving a smaller steroid dose than previous injections, resulting in less symptom relief. Other reasons that were cited were no interest in participating in research and no benefit from the previous injection. Several patients dropped out with 2 patients undergoing a total shoulder arthroplasty, 1 undergoing surgery for a labral repair, and 2 were lost to follow up. Fig. 1 summarizes recruitment and follow up.

For the study groups, Fig. 2 shows that all groups had a decrease in their SPADI scores overtime. The 20 mg group had a 23% decrease in their SPADI scores over 6 months. The 40 mg group had a decrease of 5% with their SPADI scores. The 80 mg group had a 42% decrease in their SPADI scores. No clinically significant difference ($p = 0.090$) was seen between the groups at 6 months although the 20 mg, 40 mg, and 80 mg doses all showed a reduction of SPADI from baseline at 6 months. A participant in the 20 mg group experienced one adverse event of facial flushing.

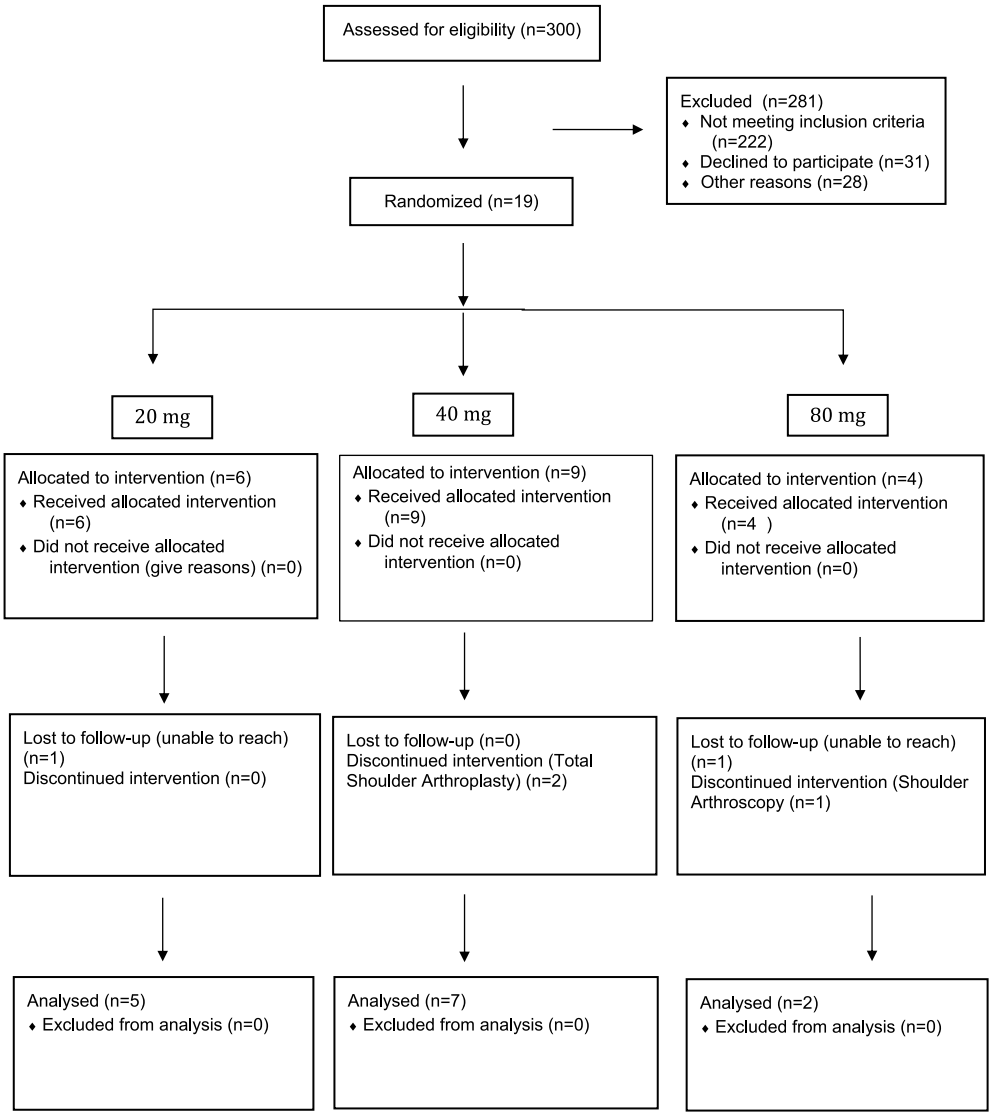

Fig. 1. 3 ARM steroid concentration RCT diagram.

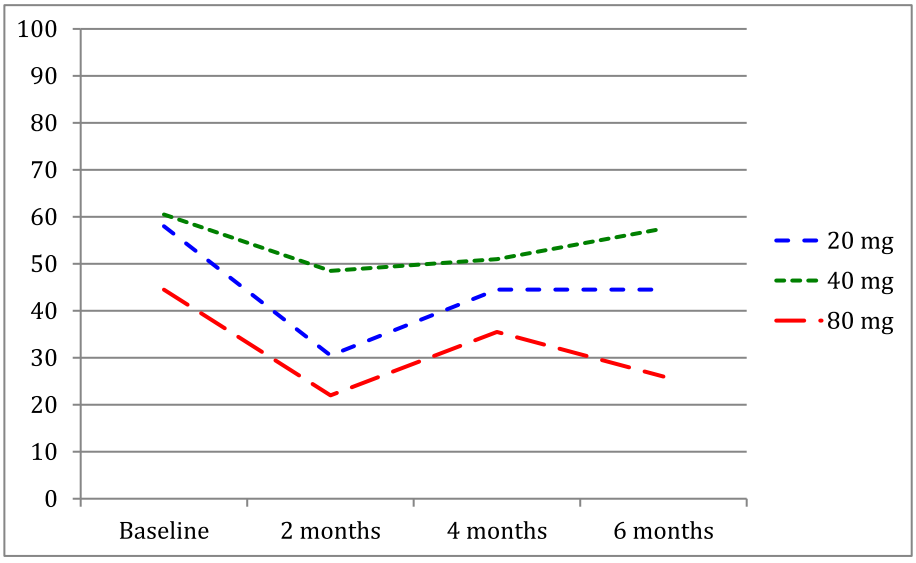

Fig. 2. SPADI Scores and Steroid Concentration over 6 months.

4. Discussion

Here we present a feasibility pilot for a double blinded randomized controlled trial evaluating pain and functional outcomes following CSI's for GH OA. This study found overall that the protocol for determining the optimal corticosteroid dose for GH OA was successful. The method for administering the injection can be done within a standard clinic schedule and be accomplished by trained providers as part of standard of care. The protocol for follow up was successful with minimal losses to follow up due to communication issues. The rate of adverse effects was low, with only one adverse side effect in the study. While the study was not significantly powered to yield clinically significant results, there were trends that pain and function improved at 2 months, but was trending up overall by 6 months. This is consistent with previous data that suggests maximum efficacy for steroid injections occurs within the first 3 months [15]. We were unable to determine if there were trends for the optimal concentration (20, 40 or 80 mg triamcinolone acetonide) of corticosteroid for improved SPADI outcomes based on the available data.

This study is the first to assess the feasibility of a double-blinded randomized control trial for determining the ideal dose of CSI for GH OA. While the majority of the protocol was successful, a refusal rate of 40% was unexpected. Perhaps more important were the reasons for refusal, with the most cited reason being that people were unwilling to risk a lower dose of steroids then they had received previously. This is significant as it is not understood how the dose of steroid impacts outcomes of pain and function, which was a purpose of this planned study. Several ways to lower the refusal rate can be considered for the consent process in future studies. Better education for patients during the explanation of the purpose for the study may help patients understand the importance of answering this question. The initial discussion to discuss participation in the study was conducted over the phone; it may be helpful to have the entire process take place in the clinical setting, where the physician performing the injection can answer questions directly. Finally, we could exclude anyone who previously received a GH injection, but researchers would need to anticipate a decrease in eligible participants necessitating a change in number needed for adequate power.

Limitations of this feasibility pilot include differences in the number of subjects randomized to each treatment group as this feasibility pilot was completely randomized until its completion. In addition, there were differences in baseline SPADI scores between treatment groups, which may have influenced our findings although this difference should have been accounted for as we compared individual outcomes between each group. Future well powered studies would need to address these differences matching baseline characteristics and taking care to randomize equally by the end of data collection. Future, larger scale studies are needed to fully assess for differences in pain and functional outcomes for GH OA to determine the ideal dose of corticosteroid for intra-articular injections. However, this feasibility study can aid in the development of those studies to increase participation and decrease an unexpectedly high refusal rate that was encountered during the implementation of this study.

5. Conclusion

Overall, this study found a feasible protocol to conduct a double-blinded randomized control trial to determine the ideal dose of intra-articular CSI for GH OA. However, an unexpectedly high refusal rate was encountered. This could be improved through more robust education during the initial consent process, conducting the discussion fully in the clinical setting, rather than over the phone in future studies, or excluding anyone who previously received a CSI. The main reason for participant refusal (concern of receiving a lower steroid dose) highlights the importance of completing a larger scale study.

Credit author statement

Cayce Onks: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Writing Original Draft, Writing Review & Editing, Visualization, Supervision.

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Declaration of competing interest

Authors declare no conflict of interest.

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