Intra-articular doxycylcine: A Novel Treatment of Adhesive Capsulitis

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RESEARCH PLAN

Specific Aims:

Adhesive capsulitis, also known as frozen shoulder, is a common condition of the shoulder joint affecting 2-5% of the adult population, and characterized by progressive, painful loss of both passive and active range of motion of shoulder[1, 2]. Individuals affected by this condition find it increasingly difficult to perform activities of daily living that require overhead movement or rotation of the affected shoulder. The natural history of frozen shoulder follows a predictable progression of symptoms, lasting from 9-24 months before complete resolution and resulting in significant loss of productivity and quality of life for those affected[3]. Despite the significant number of patients affected by adhesive capsulitis and the extensive literature focused on the progression and natural history of the condition, the true underlying etiology remains poorly understood. In light of this poor understanding of the condition, it is not surprising that a number of conservative and invasive modalities exist as accepted treatments. These include NSAIDS, oral steroids, intra-articular steroid injections, PT, and benign neglect as well as more invasive treatments such as hyrdodilation, manipulation under anesthesia, and arthroscopic capsular release[2]. These treatments have all be shown to have short-term benefit in pain relief, but none have proven to be superior nor alter the long-term natural history of adhesive capsulitis.

Over the past decade, however, there has been a growing body of literature suggesting that Propionibacterium acnes infection may play a significant role in a variety of pathological conditions affecting the native shoulder, most notably frozen shoulder[4, 5]. Our goal is to employ a treatment strategy focused on eradicating P acnes infection as a conservative treatment of adhesive capsulitis. **Through this proposal, we aim to complete a prospective randomized trial to examine the hypothesis that administration of intra-articular antibiotics effective against P acnes will prove to be a superior treatment of adhesive capsulitis as compared to current gold standard of intraarticular steroid injection.**

Specific Aim 1: Determine if intra-articular doxycycline is superior to intraarticular corticosteroid in the treatment of adhesive capsulitis.
We hypothesize that intra-articular doxycycline injection will be a more effective treatment of adhesive capsulitis than the current gold standard of intraarticular steroid injection**. Methods:** We will recruit a total of 40 patients from the Vanderbilt Sports Medicine Clinics who have been diagnosed with adhesive capsulitis and have not undergone any previous treatment. The 40 patients will be randomized, with 20 in the control group of 3 intra-articular injections of 40mg Methylprednisolone spaced every two weeks, and 20 in the experimental group of 3 intra-articular injection of 50mg doxycycline spaced every two weeks.Both groups will begin a standardized physical therapy program within a pain-free range of motion 4 weeks after the initiation of treatment. We will prospectively follow patients for one year, with follow-up at 6 weeks, 12 weeks, 6 months, and 12 months after the initiation of treatment. Outcomes will be measured using the American Shoulder and Elbow Score (ASES), which will be administered by the treating physician. Both the patients and physicians participating in the study will be blinded. **Anticipated Outcome:** We anticipate that patients treated with intra-articular doxycycline will have significantly higher ASES scores at each time point of follow-up as compared to patients treated with intra-articular corticosteroid injections.

The proposed study has the potential to make a significant and long-term impact on not only the treatment of adhesive capsulitis, but on the treatment of wide array of destructive joint disease. Over the past decade, there has been a growing body of literature suggesting a potential infectious etiology in an array of articular pathologies. Although classically thought to be the result of genetics and biomechanical forces, there is growing evidence that many pathological conditions, including osteoarthritis, degenerative disc disease, and adhesive capsulitis, may have an infectious origin[4-6]. In recent literature, Propionibacterium acnes has been identified as the potential infective pathogen underlying these conditions. This project could not only add significant evidence to support the role of P acnes in native joint dysfunction, but also introduce a potential novel treatment for these conditions, spurring new research opportunities across orthopaedic specialties.

Research Strategy

Significance: Adhesive capsulitis is a common condition of the shoulder joint affecting 2-5% of the adult population[1]. For shoulder experts, sports medicine specialists, or general orthopaedists, adhesive capsulitis is a frequent diagnosis for which patients seek care. The condition often remains symptomatic for over a year despite treatment and results in significant morbidity and loss of function for those affected[2] Despite the significant number of patients affected by adhesive capsulitis and the extensive literature focused on the natural history and treatment of the condition, the true etiology remains poorly understood and no currently accepted treatment has proven to alter its natural history.

Over the past decade, however, there has been a growing body of literature suggesting that Propionibacterium acnes infection may play a significant role in a variety of pathological conditions of the shoulder[4, 5]. P acnes is a gram-positive anaerobic bacillus that is closely associated with sebum-producing hair follicles and has been shown to preferentially colonize the shoulder and upper back[7]. Much of this literature has focused on the role of P acnes in post-operative infections, especially PJI after shoulder replacement and several authors have reported it to be the most common infecting organism after rotator cuff repair[8-10]. Recently and most significantly, however, there has been emerging evidence that P acnes may play a role in other conditions affecting the native shoulder, most notably osteoarthritis and adhesive capsulitis[4, 5]. Levy et al found that joint fluid cultures were positive for P acnes in 23 of 55 patients undergoing primary shoulder joint replacement for osteoarthritis or cuff arthropathy and who did not have previous shoulder surgery of any kind[5]. Schneeberger et al reviewed 7 patients who initially presenting with diffuse, non-localized shoulder pain and were found to have undiagnosed low-grade infections at the time of surgery[11]. None of these patients had ever undergone shoulder surgery. Of note, 3 of these 7 patients were had a pre-operative diagnosis of adhesive capsulitis and P acnes was found to be the infective organism in 5 of the 7 patients. Most relevant to the discussion of adhesive capsulitis, Bunker et al cultured synovial tissue from the shoulders of 10 consecutive patients with adhesive capsulitis undergoing arthroscopic release and found that 8 of the 10 patients had positive cultures, 6 of which grew P acnes[4]. This emerging research suggests that indolent P acnes infection could be the underlying cause of adhesive capsulitis.

To date, there have been no studies exploring whether empiric treatment of adhesive capsulitis with antibiotics effective against P acnes will lessen either the duration or severity of symptoms as compared to current treatment modalities. This project could not only add significant evidence to support the role of P acnes in adhesive capsulitis, but also introduce the first treatment modality that has potential to alter the natural history of the condition.

Innovation: There is a wide variety of currently accepted conservative and surgical options for the treatment of adhesive capsulitis. Unfortunately, none of these treatment options have been shown to shorten or alter the long-term natural history of the condition. Although some of these treatments are effective at reducing acute pain, patients must endure a prolonged course of pain, stiffness, and eventual resolution of their symptoms over the course of 12-24 months[1]. The lack of effective interventions for adhesive capsulitis can largely be explained by the illusive etiology underlying the condition. Over the past decade, however, there has been mounting evidence suggesting that P acnes infection of the shoulder joint may play a role in the onset of adhesive capsulitis[4-6]. This project could not only provide further evidence of role of P acnes in adhesive capsulitis, but more importantly introduce a novel treatment for the condition that has the potential to shorten the duration of symptoms.

Approach:

Patient Selection: We will recruit a total of 40 patients from the Vanderbilt Sports Medicine Clinics who have a diagnosis of idiopathic stage II adhesive capsulitis of the shoulder, as determined by treating physician. Inclusion criteria will be 18 years of age and older, allergy to Doxycycline or Methylprednisolone, pregnancy, diagnosis of stage II adhesive capsulitis as determined by clinical examination of the treating physician, and absence of abnormal findings on X-ray. Exclusion criteria will be diagnosis. Inflammatory arthritis or diabetes, secondary adhesive capsulitis (history of significant trauma, RTC injury, stroke), evidence of arthritis on x-ray, current infectious disease, and any previous treatment for the for adhesive capsulitis of the affected shoulder.

Materials and Methods: Patients meeting the inclusion criteria will be randomized into either the control group of 3 intra-articular injections of 40mg Methylprednisolone spaced every two weeks or the experimental group of 3 intra-articular injection of 50mg doxycycline spaced every two weeks, with 20 patients in each group. Female participants will have a urine pregnancy test done prior to the first injections. Injections will be administered by the treating physician. Both groups will begin a standardized physical therapy program within a pain-free range of motion 4 weeks after the initiation of treatment. Both the patients and physicians participating in the study will be blinded to the treatment received. The Vanderbilt Investigational Pharmacy will provide the doxycycline and the steroid solutions and will be in charge of patient randomization.

Doxycycline was select as the as the experimental intervention for this study as it is effective against P acnes and has been shown to be protective against joint damage in both in vitro and in vivo models[12-16]. Moreover, tetracylines have been shown to be safe and effective for intra-articular use in the treatment of hemophilic arthropathy in humans and in multiple animal models[17]. The decision to use doxycycline 50mg was based on the general acceptance of using 50% of the standard systemic dose for intraarticular injections of antibiotics and the known stability of the antibiotic at a concentration of 10mg/ml[18]. This dosage will provide intraarticular levels of doxycycline well above the typical minimum inhibitory concentration (MIC) for doxycycline-susceptible *P. acnes*.

Data and Safety:

An independent physician (Warne Fitch, MD) at VUMC will serve as the data safety monitor. The site will have monthly study meetings with the KSP to discuss number of eligible patients seen during the previous month, how many of them were approached for participation and how many of them consented or refused to participate. Protocol deviations and adverse events will be reviewed. The accumulative findings will be reported on an annual basis to the DSM.

All adverse events will be recorded and reported upon finding them. All serious adverse events will be reported to the Data Safety Monitor (DSM) within 48 hours of identification. The DSM will then review them with the PI within 72 hours and will notify the VUMC IRB Department within 10 business days.

Formal DSM reviews and reports will be conducted annually.

Data Collection: Patients will be followed prospectively for one year, with follow-up at 6 weeks, 12 weeks, 6 months,, and 12 months after the initiation of treatment. Outcomes will be measured using the American Shoulder and Elbow Score (ASES), which will be administered by the treating physician at each follow-up visit. The ASES questionnaire was developed to provide a standardized method for evaluating shoulder function and has been validated in patients with any array of shoulder pathologies[19-23].

Data Analysis: ASES scores at each time point in follow-up will be input into SPSS software (SPSS Inc, Chicago, IL) for statistical analysis. Statistical tests for nonparametric variables will be used. Paired *t* tests will be used to compare paired groups for continuous variables. Independent *t* tests will be used to compare different treatment regimens. Level of significance will be set at $P \leq .05$.

Potential Problems: Potential problems include possible allergic reactions to medications, or possibly introducing infection, which would be considered extremely rare. Patients enrolled will be carefully followed.

PROJECT TIMELINE

0-6 Months	6-12 Months	12-18 Months	18-24 Months	24-26 Months
Patient enrollment, randomization, initiation of treatment				
Data collection at each follow-up time point				
		Data analysis		
			Manuscript preparation	

HUMAN SUBJECTS

Description of Study:

We will recruit a total of 40 patients from the Vanderbilt Sports Medicine Clinics who have been diagnosed with adhesive capsulitis and have not undergone any previous treatmentThe 40 patients will be randomized, with 20 in the control group of 3 intra-articular injections of 40mg Methylprednisolone spaced every two weeks, and 20 in the experimental group of 3 intra-articular injection of 50mg doxycycline spaced every two weeks. Both groups will begin a standardized physical therapy program within a pain-free range of motion 4 weeks after the initiation of treatment.. Both groups will begin a standardized physical therapy program within a pain-free range of motion 4 weeks after the initiation of treatment. We will prospectively follow patients for one year, with follow-up at 6 weeks, 12 weeks, 6 months, and 12 months after the initiation of treatment. Outcomes will be measured using the American Shoulder and Elbow Score (ASES), which will be administered by the treating physician. Both the patients and physicians participating in the study will be blinded.

Potential risks and complications:

Because patient data is being collected there is a slight risk of a breach of confidentiality. To reduce this risk, most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases and surveys. The data obtained and stored in Redcap will only be accessible by research personnel. All study data will be maintained for 6 years following study completion. Following this 6 year period, the Redcap database will be archived and all physical study forms will be disposed of in shred-it confidentiality bins provided by VUMC.

The drugs used in this study are not narcotics or habit-forming but can have side effects. The treating physician will screen for any condition that would increase the chance for the patient to have an unwanted side effect. However, there is a small possibility that an injection of these medicines can be painful and cause bleeding or infection.

Statement of confidentiality:

During this study, every attempt will be made to keep the patient's protected health information (PHI) private. Most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases and surveys. The data obtained and stored in Redcap will only be accessible by research personnel. Any data sent to non-key study personnel for statistical analysis will be de-identified (dates will be shifted using a Redcap feature). Any physical study forms (ex. consent documents, surveys) will be kept in a locked cabinet in the Vanderbilt Orthopaedic Institute Administrative Offices. All study data will be maintained for 6 years following study completion.

Following this 6 year period, the Redcap database will be archived and all physical study forms will be disposed of in shred-it confidentiality bins provided by VUMC.

Allowance for non-prejudicial withdrawal for investigation:
Participation in this study is completely voluntary. If the study participant wishes to be withdrawn from the prospective portion of this study following consent, they may do so by letting the key study personnel know they withdraw their consent. All data collected up to the point of the patient's study withdrawal will be included in study analysis.

Liability and hold harmless clause:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then the patients and/or their insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give the patient money for the injury.

APPENDIX 1: **ASES Shoulder Assessment (Patient Evaluation)**