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Brief Title: Dysphagia Following Anterior Cervical Spine Surgery; Steroid vs Saline (DysDexVSSal)

Title: The Effects of Perioperative Steroids on Dysphagia Following Anterior Cervical Spine Surgery: A Randomized, Prospective, Double-Blind Study

The Effects of Perioperative Steroids on Dysphagia Following Anterior Cervical Spine Surgery: A Randomized, Prospective, Double-Blind Study

This prospective, randomized, double blind, controlled study evaluates the effect of perioperative IV steroids versus saline on swallowing after anterior cervical spine surgery. The specific aim of this study is to determine if perioperative steroids can positively influence post-operative swallowing following anterior cervical surgery.

Literature Review

Anterior approaches to the cervical spine were developed in the late 1950s and have been a mainstay of operative treatment for cervical disorders. The most common etiology of cervical spine problems requiring surgery is degenerative in nature; however, traumatic, neoplastic, infectious, and deformity-based conditions that require surgery are often approached anteriorly as well. The common types of procedures include anterior cervical discectomy and fusion (ACDF) at one or more levels, anterior cervical corpectomy and strut grafting at one or more levels, hybrid reconstruction following corpectomy plus ACDF, and more recently, total disc arthroplasty. All of these procedures utilize the same operative dissection to expose the anterior cervical spine. They also all require retraction of the esophagus often for several hours in the more complex cases.

Dysphagia is the term for symptomatic swallowing difficulties in patients. Swallowing is known to be a complex neuromuscular function with innervation from the pharyngeal plexus, the ansacervicalis, and cranial nerves IX, X, and XII. Virtually all patients will have some swallowing difficulty immediately after an anterior cervical spine procedure (1). The primary cause of this dysphagia is not believed to be denervation from the surgical approach but rather edema and late fibrosis in the esophageal tissue from the pressure of retractors (2,3). This has been shown histologically in a sheep study done by Cavusoglu et al (4). Other factors contributing to postoperative dysphagia include the presence of an anterior plate, the number of operative levels, higher levels of the cervical spine (such as C3-C4), duration of surgery, hematoma, and female gender (5-8).

Despite the anterior approach for cervical surgery having been popular for decades, it is only in the last several years that better studies have clarified the problem. In 2002, Bazaz et al. documented higher percentages of dysphagia months after surgery than had previously been known (9). These investigators obtained patient-reported symptoms at various time points up to one year following anterior cervical surgery. They developed a scale of none, mild, moderate, and severe symptoms of dysphagia and reported on 249 patients. The incidence of symptomatic swallowing difficulty was a surprising 50% at one month, 32% at two months, 18% at six months, and 12.5% at 12 months. Moderate to severe symptoms were still noted in 4.8% of patients six months post-operatively. Similarly, Riley et al. published on a large Cervical Spine Research Society cohort of 534 patients. Their data also showed a substantial percentage of symptoms three months post-operatively (29%). Six percent of patients still had some dysphagia 24 months post-operatively (10).

Steroids have long been used clinically for their physiologic effect of decreasing soft tissue edema. This effect has been utilized commonly in patients with spinal cord injury, cerebral swelling, and various pulmonary conditions. Some studies suggest a decrease in upper airway edema following cervical spine surgery, (11)though a randomized controlled trial done by Emery et al. found no benefit from steroids in the multi-level corpectomy patient population (12). Lee et al did a randomized study regarding intraoperative steroid soaked collagen sponges and their effect on prevertebral soft tissue swelling (13). The measurable soft tissue edema was decreased in the early time periods in the steroid group, and lower VAS (visual analog scale) scores regarding odynophagia were documented in the steroid group as well. Our study will use intravenous steroids and use two established dysphagia questionnaires for a more focused, in depth investigation of post-operative swallowing symptoms.

Steroids can cause hyperglycemia in predisposed patients such as diabetics and chronic use can suppress the immune system. High doses for longer periods of time can also result in avascular necrosis of the femoral head. In very short treatment periods such as a few days, the safety profile for steroid use is extremely high and indeed remains a common treatment option in spine patients as well as in many other disciplines. If steroids are beneficial in this clinical setting, it could lead to greater patient satisfaction, decreased hospital length of stay, and perhaps avoid permanent symptoms of dysphagia. If steroids are of no benefit than decreased peri-operative use could result in cost savings and avoid potential complications of the drug.

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Research Design

This investigation is a prospective, randomized, double-blind, controlled trial testing peri-operative steroids versus saline and the effect on swallowing after anterior cervical spine surgery. Persons between the ages of 18 and 80 undergoing anterior cervical decompression and stabilization procedures for degenerative conditions are eligible for the study. This would include persons undergoing anterior cervical discectomy and fusion (ACDF), hybrid constructs, corpectomy(ies), and disc arthroplasty.
Persons excluded from the study include those with major trauma, neoplastic, or infectious conditions requiring surgery. Also excluded are persons undergoing anterior-posterior operations, those with a history of previous anterior cervical spine surgery, any one requiring a halo vest, persons on chronic steroids, and persons remaining intubated postoperatively.

Swallowing symptoms will be measured using the patient reported Bazaz scale and the Dysphagia Short Questionnaire. Swallowing data will be obtained pre-operatively, one day and two days post-operatively and then one week, two weeks, four weeks, three months, six months, and one year post-operatively. Other data to be collected for analysis includes patient comorbidities, levels and type of surgery, intra-operative fluids, estimated blood loss, type of retractors, type of brace if any, length of stay, and other surgically related complications. Patient clinical outcomes will be captured using our web-based progress reports.

Participants in this study will complete the QoL-12, Neck Disability Index, and Visual Analog Scale questionnaires electronically pre-operatively and at one month, three months, six months, and one-year post-operative time points. This outcome data will help us analyze the swallowing function or symptoms with the overall clinical course of the participants enrolled in this study.

Inclusion Criteria:
• Elective anterior approach to subaxial cervical spine (C3 - T1)
• Ages 18-80

Exclusion Criteria
• Traumatic or tumor etiologies
• undergoing anterior-posterior operations
• neoplastic, or infectious conditions requiring surgery
• a history of previous anterior cervical spine surgery
• any patient requiring a halo vest
• patients on chronic steroids
• patients remaining intubated post-operatively (please see more under risks below)
• less than 18 years of age
• pregnant women
• no phone

Procedures
Persons who have chosen to undergo anterior cervical spine surgery will be seen at the clinic for a pre-operative visit. The surgeons on the protocol will discuss the study and the subjects will be given the opportunity to participate. If the subjects agree to participate, a consent form will be administered by a member of the research team. The Bazaz and Dysphagia Short Questionnaire will be administered to subjects at this visit prior to surgery and again at Day 1, Day 2, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months after surgery. If the subject does not come for a clinic visit at the follow up times, he/she will be called to answer the questions on the surveys. The windows-of-time in which subjects may be called after discharge include: for follow up for week 1 and week 2, two days before or after the actual day of 1 or 2 weeks; for week 4, three days before or after the actual day of 4 weeks; for 3 months and 6 months, a week before or after the actual date of 3 or 6 months; for 1 year, 2 weeks before or after the actual date of 1 year. Subjects will be randomized to either the steroid administration group or the saline administration group. Subjects randomized to the experimental (steroid) group will receive 0.3 mg/kg of intravenous dexamethasone within one hour of the incision, then 0.15 mg/kg every eight hours (window of time 45 minutes on both ends of the eight hour time, e.g. if the time is 8 pm, the dose could be given from 7:15 pm through 8:45 pm) for two doses. This dosage is approximately 20 mg, 10 mg, and 10 mg of dexamethasone. Subjects in the control (saline) group will receive a similar volume of saline on the same schedule for three doses. This is a double-blind trial; the surgeon (and anesthesiologist) and the subject will not know what group assignment the subject has received. The in-patient pharmacy will generate IV bags that are labeled for the study but that are blinded as to medication/saline labels. Randomization will be performed by the satellite pharmacist outside of the operating room. This person will also supply the study drug.

Sample Size
70

Sample Size justification
Our power analysis indicates 64 subjects with 32 in each arm is enough to give us 81% power to reject the null hypothesis. We are adding an additional 10% to that number as we expect to have a loss to follow up of approximately 10%.

Data Analysis
Power and sample size calculations are based on the presence or absence of dysphasia at 2-weeks. Based on a literature review we postulated that 50% of the subjects in the control arm would experience mild, moderate or severe dysphasia. If that figure can be improved to the point where just 20% of the subjects are similarly affected, then that, in our opinion, would represent clinical success. Under the above scenario, 32 subjects in each arm would give us 81% power to reject the null hypothesis. We plan to analyze the data in two ways. First, we will look at the time-to-event where the event is "no dysphasia" in a discrete time survival model. Second, we will use a repeated measures ordinal categorical model to assess the effect of steroid/control in a generalized linear model. We have an electronic database that we will use to track patient outcomes. If subjects are unable to return to clinic, they will be able to complete the database questionnaires online. Our clinical research coordinator will also be able to contact subjects via phone to complete the Bazaz scale and Dysphagia Short Questionnaire.

Potential Risks/Discomforts/Privacy

Completion of the Bazaz scale and Dysphagia Short Questionnaire may cause some discomfort. The only expected side effect, in the group receiving steroids, would be possible elevation of serum glucose levels in diabetic subjects. The serum glucose levels in diabetic subjects will be monitored postoperatively with routine postoperative laboratory testing. All other procedures are standard of care.

Potential subjects will be recruited/consented for the study in private rooms at the Physician Office Center (POC) when they come for their History and Physical visit prior to surgery. All HIPAA safeguards are in place at the POC. Subjects will not be contacted outside of what is necessary for the research study.

Potential Benefits

To Subject: The group randomized to steroid administation may experience less or no dysphagia two weeks after the surgery.

To Society: The benefit to society will be publishing the results of the study regardless of whether we see improvement in dysphagia after administration of steroids or no improvement. Other surgeons performing this type of surgery will benefit knowing our results.

Risk to benefit ratio: The benefit of knowing whether administration of steroids causes less dysphagia in anterior cervical spine surgery as opposed to saline administration, outweighs the risk/discomfort of completion of surveys measuring the prevalence and

severity of dysphagia and the possibility of hyperglycemia in patients with diabetes who will be routinely monitored and treated during surgery and the course of their hospital stay.

Consent Procedures

Potential subjects who have chosen to undergo anterior cervical spine surgery will be seen at the clinic for their History and Physical visit. The surgeons on the protocol will discuss the study and the subjects will be given the opportunity to participate. If the subjects agree to participate, a consent form will be administered by a member of the research team signed by the subject and research team member and a copy of the signed consent form will be given to the subject. The Bazaz survey and the Dysphagia Short Questionnaire will be administered to subjects at this History and Physical visit prior to surgery and again at Day 1, Day 2, week 1, week 2, months 1, 3, 6, and 12 after surgery. Subjects will be randomized to either the steroid administration group or the group receiving saline. Subjects will undergo anterior cervical spine surgery per standard of care.

Confidentiality

Subjects will be recruited/consented in private rooms of the POC. The Bazaz scale and Dysphagia Short Questionnaire will have assigned numbers attached to the outcome tools instead of any identifying information from the subject. Scores from the electronic tools used to gather Health Progress Report (outcomes) data will be placed in the excel spreadsheet with the assigned number. The number, corresponding to the patient, will be kept on a password protected computer on an excel spread sheet. The surveys will be kept in a locked file cabinet, in a locked room when the research team members are not present, in the department of Orthopaedics, third floor health sciences. All HIPAA safeguards are in place.

No cost and no payment to subjects

No radioactive materials will be used and there will be no exposure to infectious agents.

No advertisements will be used to promote the study.