**Research Protocol**

**Draft Date:** 9/16/12

**Title:** Efficacy of Oral Methylprednisolone in Reducing Post-operative Dysphagia Following Anterior Cervical Discectomy and Fusion (ACDF) with rhBMP-2

**Shortened Title:** Efficacy of Oral Methylpredisonone in Reducing Dysphagia Following ACDF.

Description of Research Study

**Investigators:**

John Heller MD, Professor of Orthopaedic Surgery

Gerald Rodts MD, Professor of Neurological Surgery

John Rhee MD, Assiociate Professor of Orthopaedic Surgery

Michael Murray MD, Fellow in Spine Surgery

Ashton Mansour MD, Resident in Orthopaedic Surgery

**Abstract:**

Anterior cervical discectomy and fusion is a widely performed, successful, and reliable procedure used in the treatment of cervical radiculopathy and cervical myelopathy. rhBMP-2 may be used as an adjunct to promote fusion in patients with risk factors for pseudarthrosis. rhBMP-2 has been associated with increased swelling of the anterior cervical soft tissues which may lead to an increased rate of post-operative dysphagia. In this study we seek to determine both retrospectively and prospectively if the administration of a post-operative tapered dose of oral methylprednisolone decreases the rate of dysphagia compared to either patients that have undergone ACDF with rhBMP-2 without a course of post-operative oral methylprednisolone, or those that have undergone ACDF without the use of rh-BMP-2. In the retrospective portion of the study all patients in a one-year period (2011-2012) that underwent ACDF at our institution will receive a 14-point subset of the SWOL-QOL questionnaire. They will complete three copies of the questionnaire, one that retrospectively reports their level of dysphagia prior to surgery, one in the post-operative period (2 days – 2 weeks post op) and one that assesses their current level of dysphagia. The results of these questionnares will be compared between the 3 groups.

The prospective observational portion of the study will involve enrolling 30 patients into each of the above listed surgical/post-operative protocols. This portion of the study is observational in that three separate surgeons within our institution currently endorse one of the above surgical and post-operative protocols. 30 consecutive patients from each of the surgeons would be offered enrollment in the study. These patients would be given a 14-point subset of the SWOL-QOL to be completed pre-operatively, 1 day post-op and at every normally scheduled outpatient visit up to 1 year post-operatively. In addition, patient specific factors including age, sex, specific procedure (1 vs 2 level ACDF), surgical indication and smoking history. Pairwise t-tests will be performed in order to detect differences between groups in terms of SWOL-QOL score as well as the other patient-specific parameters that are analyzed.

**Introduction/ Background literature:**

Anterior cervical discectomy and fusion (ACDF) is a procedure that is frequently indicated in the surgical management of cervical radiculopathy and cervical myelopathy. This procedure is performed commonly with over 200,000 surgeries performed in the US alone in the 1990s (ref). The frequent utilization of this procedure is largely due to the reliable and successful results, which have been reported to exceed > 90% good or excellent results [[1](#_ENREF_1)]. The high rate of clinical success following ACDF surgery is in part due to the high rate of fusion that is achieved when allograft is used as the source of bone graft (91-97-%) ([[2-4](#_ENREF_2)]). However, fusion is more challenging in patient’s that have one or more risk factors for pseudarthrosis including smokers[[5](#_ENREF_5)], patients with osteoporotic bone, multiple level surgery, and revision surgery cases. rhBMP-2 has been used In these instances to enhance the probability of a successful fusion with successful fusion rates of up to 100% have been reported.[[6](#_ENREF_6), [7](#_ENREF_7)]. However, the initial use of rhBMP-2 in the anterior cervical spine was followed by multiple reports of increased complications including the delayed onset of airway edema and the formation of seroma at the surgical site [[8-10](#_ENREF_8)]. Importantly these complications were seen in the setting of levels exceeding 2mg of rh-BMP-2 per cervical spine level. The current use of significantly lower levels of rhBMP-2 (approximately 0.5mg per level), has resulted in a decrease in complications comparable with control groups while maintaining the enhanced fusion rates [[6](#_ENREF_6), [11](#_ENREF_11)]. Despite the decrease in rate of airway compromise with lower doses of BMP, it is possible that the use of current doses of rhBMP-2 may potentially lead to higher rates of swallowing difficulty (dysphagia) when compared to patients that underwent ACDF with allograft bone is used in isolation as a source of bone graft. In order to prevent this hypothetical increased risk of dysphagia following the use of BMP, the practice of prescribing a post-operative tapered course of oral methylprednisolone has been suggested. In our investigation, we attempt to determine in both a retrospective as well as prospective fashion whether a post-operative course of oral methylprednisolone following ACDF with rhBMP-2 decreases the incidence of dysphagia compared to the use of rh-BMP-2 without an oral steroid taper, and we also compare this rate with a control group of patients that underwent and ACDF with allograft bone alone as the source of bone graft. Up to this point, these comparisons between the above surgical protocols in respect to dysphagia have not been performed.

**Objectives:**

The objective of this study is to determine if the addition of a post-op oral methylprednisolone taper following ACDF with rhBMP-2 will decrease the rate and severity of dysphagia when compared to patients undergoing ACDF with rhBMP-2 without oral methylprednisolone. This study will also compare post-operative dysphagia in patients taking post-operative oral steroids with a control group (those undergoing ACDF without the use of rhBMP-2 (patient’s undergoing ACDF with allograft bone as the source of bone graft)).

The primary outcome measure of this study is the score on the 14- question subset of the validated SWOL-QOL questionnaire, an standardized outcome measure of dysphagia.

**Study Design and Methods:**

The study investigates the efficacy of an oral tapered dose of methylprednisolone following ACDF with allograft bone filled with rhBMP2, compared to patients undergoing ACDF with allograft bone filled with rhBMP-2 without post-operative oral steroids as well as patients undergoing ACDF with allograft bone alone, without the use of rhBMP-2.

We have two arms of patients in this investigation. The first arm of patients constitutes the “retrospective” portion of the study. These patients will include those that underwent ACDF with rhBMP-2 with an oral corticosteroid taper, those that underwent ACDF with rh-BMP2 without an oral steroid taper and those that underwent ACDF with allograft bone as the source of bone graft at least 1 year ago, but less than 2 years ago. These patients will be identified by reviewing the CPT codes for anterior cervical discectomy and fusion at the Emory Spine Center between 1-2 years ago. The identified patients will be called and consent will be obtained for their inclusion in the study. Each patient that chooses to enroll in the study will be sent three copies of a 14-point portion of the validated SWOL-QOL measure of dysphagia. The patient will be asked to answer one copy of the 14-point questionnaire in reference to the point in their life prior to their ACDF. The second copy of the questionnaire will be answered in regard to their status in the immediate post-operative period (2 days – 2 weeks) post-operatively. The third copy will reflect their current status in regard to dysphagia. The results of these questionnaires will be compiled and compared between the three different surgical / post-operative protocols that are being evaluated.

The second “arm” of the study is the observational prospective portion. In this portion of the study we will monitor 3 groups of patients (30 patients in each group); one with BMP plus a course of post-operative oral steroids, one that underwent ACDF with BMP and did not receive oral steroids post-operatively as well as a control group that undergoes ACDF without the use of BMP. This portion of the study will be observational in nature that at our institution the three attending surgeons involved in this study each currently perform one of the three operative/-post-operative protocols listed above as their standard protocol. Therefore, none of the patients will be receiving an experimental protocol and there will be no randomization process. These three groups will be complete the same 14-question subset of the SWOL-QOL as the patients in the retrospective arm of the study. They will receive this questionnaire pre-operatively, the first day following surgery, and at their regularly scheduled 2 week, 6 week, 3 month, 6 month and 12 month post-operative follow up visits. The patients in each group will compared with each other at each time point in order to determine if the use of a post-operative course of oral steroids is useful in minimizing post-operative swallowing difficulties following ACDF with BMP.

**Statistical analysis:**

Scores on the 14 point subset of the SWOL-QOL will be compared between the 3 study groups using pairwise Student T-test analysis. Pairwise T-tests between each of the three groups (for continuous variables) and Chi squared analysis (for categorical variables) will be used to determine if a statistically significant difference exists between the groups in terms of the patient specific factors that are also collected and analyzed (age, sex, smoking status, BMI, number of levels undergoing ACDF, primary vs revision surgery).

**Sample size determination and power analysis:**

Unfortunately post-operative rates of dysphagia have been widely reported with rates of 5-60% following ACDF without the use of rh-BMP. Given the wide range of reported post-operative dysphagia rates, an accurate power analysis was not possible for this study. As a result, for the prospective portion of the study we selected 30 patients per observational group which is a sample size commensurate with other published articles on this topic.

**References:**

1. Bohlman, H.H., et al., *Robinson anterior cervical discectomy and arthrodesis for cervical radiculopathy. Long-term follow-up of one hundred and twenty-two patients.* J Bone Joint Surg Am, 1993. **75**(9): p. 1298-307.

2. Miller, L.E. and J.E. Block, *Safety and effectiveness of bone allografts in anterior cervical discectomy and fusion surgery.* Spine (Phila Pa 1976), 2011. **36**(24): p. 2045-50.

3. Samartzis, D., et al., *Comparison of allograft to autograft in multilevel anterior cervical discectomy and fusion with rigid plate fixation.* Spine J, 2003. **3**(6): p. 451-9.

4. Fraser, J.F. and R. Hartl, *Anterior approaches to fusion of the cervical spine: a metaanalysis of fusion rates.* J Neurosurg Spine, 2007. **6**(4): p. 298-303.

5. Hilibrand, A.S., et al., *Impact of smoking on the outcome of anterior cervical arthrodesis with interbody or strut-grafting.* J Bone Joint Surg Am, 2001. **83-A**(5): p. 668-73.

6. Baskin, D.S., et al., *A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate.* Spine (Phila Pa 1976), 2003. **28**(12): p. 1219-24; discussion 1225.

7. Lanman, T.H. and T.J. Hopkins, *Early findings in a pilot study of anterior cervical interbody fusion in which recombinant human bone morphogenetic protein-2 was used with poly(L-lactide-co-D,L-lactide) bioabsorbable implants.* Neurosurg Focus, 2004. **16**(3): p. E6.

8. Perri, B., et al., *Adverse swelling associated with use of rh-BMP-2 in anterior cervical discectomy and fusion: a case study.* Spine J, 2007. **7**(2): p. 235-9.

9. Shields, L.B., et al., *Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion.* Spine (Phila Pa 1976), 2006. **31**(5): p. 542-7.

10. Smucker, J.D., et al., *Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine.* Spine (Phila Pa 1976), 2006. **31**(24): p. 2813-9.

11. Dickerman, R.D., et al., *rh-BMP-2 can be used safely in the cervical spine: dose and containment are the keys!* Spine J, 2007. **7**(4): p. 508-9.