

Bone Marrow Aspirate Concentration in Posterior Cervical Fusion

Specific Aim:

1) Measure the rate of bony fusion in high-risk patients undergoing posterior cervical decompression and fusion.

Hypothesis: Bone marrow aspirate concentration combined with locally harvested autograft results in equivalent rates of bony fusion, as compared to current best practice in high-risk patients undergoing posterior cervical decompression and fusion.

Outcome Measures

Primary Outcome Measures: Rate of fusion – (6, 12, and 24 months) *Rate of fusion will be assessed by flexion extension X-rays at routine follow-up, translation method (<2mm) and/or by computed tomography (CT) scan at 2 year post-operatively.*

Secondary Outcome Measures: Short Form 36 (SF-36), Neck Disability Index (NDI), Myelopathy Disability Index (MDI), and modified Japanese Orthopedic Association score (mJOA) (pre-operative, 3 months, 6 months, 12 months, and 24 months), rates of intraoperative and post-operative complications, and rates of reoperation.

Significance and Biological Relevance: Spine surgery has increased substantially in the U.S. during the past decade, with an estimated 100,000 patients undergoing cervical procedures annually.¹ As the demographics of an aging population begin to increase their utilization of healthcare resources, surgeons will undoubtedly be faced with an increasing number of high-risk patients. Osteoporosis, rheumatoid arthritis, smoking, and obesity have all been shown to be significant risk factors for surgical complications following spinal arthrodesis.^{3,5,6} Nicotine has a direct inhibitory effect on autologous cancellous bone graft revascularization, significantly increasing the rate of bony non-union.^{3,18} Similarly, obesity has been demonstrated to represent a significant risk factor for subsequent pseudoarthrosis and has been linked to nearly a 100% higher in-hospital complication rate.^{10,11}

Achieving solid bony fusion following cervical arthrodesis has long been considered the most important primary outcome measure. Non-union or pseudoarthrosis following cervical instrumentation can lead to persistent neck pain and/or recurrence of myeloradiculopathy.¹⁶ The incidence of bony fusion is affected by both patient systemic factors and local biologic environment. Significant resources have been invested into studying local environment following spinal arthrodesis, with a particular focus on high-risk patients.^{7,14,15} While rhBMP has been demonstrated to improve osseous fusion in both pre-clinical and clinical studies, increasing concerns over safety and cost efficacy have resulted in a decrease in rhBMP utilization.

Autogenous iliac crest bone graft has long been considered the current “gold standard” for use in spinal fusion surgeries because its osteogenic, osteoinductive, and osteoconductive properties are ideal for promoting fusion from a biological perspective.² However, there are numerous well-acknowledged complications associated with harvesting iliac crest, such as chronic pain, nerve injury, and pelvis fracture. To circumvent these complications, allograft bone graft alone, was proposed as a viable alternative, but it has its own shortcomings due to lack of osteoinductive factors.

Bone marrow aspirate (BMA) concentration represents a potential osteoinductive alternative to rhBMP.² BMA can be easily obtained with a needle or through a minimal incision and it contains hematopoietic cells and mesenchymal stem cells (MSC).¹² BMA can be used immediately during the operation, usually in combination with a carrier such as cadaveric allograft or demineralized bone matrix, or can be subjected to further processing to concentrate MSCs, platelet-rich plasma, or CD34+ cells. MSCs exhibit potency to differentiate into mesenchymal tissues, including bone, cartilage, muscle and adipose tissue.⁴ Multiple authors have reported good clinical outcomes with difficult osseous non-unions^{8,9,17} of the extremities or jaw, yet the quality of evidence supporting the efficacy of BMA concentration during surgical management of degenerative spine disease remains limited.^{2,13} With the recent shift in medicine towards a value-based system, demonstration of cost-effectiveness in tandem with clinical efficacy is of paramount importance. The results of this study will provide not only benchmark data for further modeling an incremental cost-effectiveness ratio, but more importantly determine whether bone marrow aspirate concentration can reliably improve bony fusion in a high risk patient population undergoing posterior cervical arthrodesis.

Approach: A prospective single institution non-blinded randomized trial. Patients with symptomatic cervical myelopathy or radiculopathy amenable to management with a posterior cervical decompression and fusion will be recruited to enroll in the study in either the outpatient or inpatient setting by an orthopaedic or neurosurgery physician. As part of standard

of care pre-operative work-up patients will undergo cervical MRI and or cervical CT myelogram with plain cervical X-rays, in addition to a detailed physical examination, demographic data and outcomes questionnaires, including the Neck Disability Index (NDI), Short Form 36 (SF-36), (Myelopathy disability index (MDI), and modified Japanese Orthopedic Association (mJOA) score). These outcomes measure sensibility, motor strength, bladder function and one's ability to perform specific tasks such as rising from a chair, performing fine-motor tasks and personal hygiene practices. All pre-operative imaging again is done as part of the standard of care and often times is done prior to patient referral for surgical consultation

Inclusion criteria will include cervical alignment allowing management with a posterior approach. Post-operative X-rays scans will be obtained at the 6-week, 12 week, 6-month, 12 –month and 24 month time points as part of the standard post-operative assessment. Detailed physical exams and patient reported questionnaires (NDI, SF-36, MDI, mJOA) will be obtained at these follow-up points.

100 consecutive high-risk patients who meet the following inclusion criteria: are 18-75 years of age, require a cervical spine MRI as part of their standard of care show evidence of CSM, and have cervical alignment allowing posterior instrumented fusion. High-risk will be defined as having a diagnosis of rheumatoid arthritis, osteoporosis, current smoker, or BMI >30. Patients will be excluded if they have any MRI incompatible devices, have any prior cervical instrumentation, require an instrumented anterior cervical fusion, or have an underlying neurological condition affecting the cervical spine (MS, ALS, HIV).

Patients will be sequentially randomized to one of two treatment groups. Group I, will receive current best practice for posterior instrumented fusion (locally harvested autograft, demineralized bone matrix, and cadaveric allograft). Group II, will receive locally harvested autograft and 20 cc of bone marrow aspirate concentration. To assist with analysis, we will collect information from patients' hematology results, obtained per their standard of care pre-operative workup. All patients will be treated post-operatively at the discretion of the treating surgeon. All patients will follow-up at 6 weeks, 3 months, 6 months, 12 months, and 24 months. At the 6, 12, and 24-month follow-up all patients will undergo flexion/extension X-rays, fusion will be defined as less than 2 mm or motion. A cervical spine CT may also be obtained at 24 months on all patients to assess fusion at the discretion of the treating surgeon. All radiographic assessments of fusion will be made by a Washington University staff radiologist, blinded to patient treatment.

Cellular Analysis: Would consist of bone marrow aspirate and bone marrow aspirate concentration total cell and nucleated cell counts performed on all patients from Group II. Analysis will be performed on 1 cc of aspirate and aspirate concentration harvested at the time of surgery. Additionally, we will measure Hematopoietic stem cell and colony-forming unit fibroblast counts and BMP-2 levels. All cellular analyses will be performed by a hired third party (Immune Disease Institute, Boston, MA) blinded to the study.

Eligibility Inclusion Criteria: Age 18 and 75, able to cooperate in the completion of standardized outcome measures (SF-36 & NDI), willing and able to comply with study protocol.

Eligibility Exclusion Criteria: Pre-existent neurologic disorder or mental disorder that would preclude accurate evaluation (psychiatric disease, Parkinson's disease, Alzheimer's disease), history of previous anterior cervical fusion at the operative site, pregnancy, active malignancy, history of previous posterior cervical decompression.

Data Management and Analysis

Data will be handled in a manner that complies with federal guidelines. Data will be stored on servers maintained by Washington University School of Medicine. This data will be password protected and only approved members of the research team will be granted access. All data management will be performed by a hired third party from Washington University Center for Clinical Studies. Case report forms (CRFs) will be managed using Redcap, a commercially available, web-based data management system. CRFs are completed by the Data entry for the study is web-based. CRFs are completed by the principle investigators and saved to the Redcap server site. All data is readily available for transfer to excel format for statistical analysis and interim evaluations.

Outcome assessments for the primary outcome measure (radiographic fusion) will be provided by staff radiologists of Washington University. The radiologist will be blinded to the clinical treatment received by each patient. Patients will provide completed SF-36 and NDI data at clinical follow-up. This data will be recorded directly by the

Center for Clinical Studies, while all statistical analysis will be performed by Dr. Michael Wallendorf (Biostatistics). All Staff members will randomly audit and verify 10% of the data using graphical, logic and consistency checks applied at several stages of data processing. Data that are manually collected during testing will be entered using forms designed to resemble the CRFs for enhanced accuracy.

Power Analysis: Based on our secondary outcome measures (SF-36 and NDI) preliminary estimates suggest a sample size of 50, per group, will provide greater than 80% power. This estimate was generated by the Department of biostatistics, Washington University to account for variance in the outcome score of SF-36 and NDI. It is anticipated that some patients will achieve a stable asymptomatic non-union, while some patients may fail to achieve any meaningful improvement in SF-36 and NDI scores, despite achieving solid bony fusion. Power estimates were based on a repeated measures analysis of variance (ANOVA) using PowerLib 2.02.

Timeline and Expectations: The proposed study will take 3.5 years to complete (TABLE 1). Patient recruitment will occur in a consecutive randomized fashion as described in the experimental design. Enrollment will occur during the initial 12 months and patients will be followed clinically until 2 years post-operatively. We hypothesize the results from this study will provide supporting evidence that BMAC is equivalent to the current best practice for posterior instrumented fusion in a high risk patient population.

Months	1-12	12-24	24-36	36-42
Recruitment & 1 st Assessment	X			
Surgery Group I & II	X	X		
6 week postoperative assessment	X	X		
3 month postoperative assessment	X	X		
6 month postoperative assessment	X	X		
12 month postoperative assessment		X	X	
24 month postoperative assessment			X	X
Data Analysis/Reporting Results				X

Safety monitoring plan: A Data and Safety Monitoring Committee (DSMC) will be established to address issues related to personal health information and adverse events. Each patient will be reviewed by the DSMC when third of the projected number of patients have received treatment (meet when 33, 66 and 100 patients have received treatment). The DSMC will consist 3 physicians, Dr. Ralph Dacey (Neurosurgery), Dr. Robert Grubb (Neurosurgery), and Dr. Colin Derdeyn (Neuroradiology). Reportable events will be submitted according to IRB guidelines. The same will be reported to NIH. The DSMC will meet after 33, 66 and 100 patients have received treatment to ensure ongoing safety assessments for the duration of the study. Should there be a serious adverse event that occurs that increases the risks to the participants, the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed. It should be noted that the funding institute and center (IC) may wish to establish a Data and Safety Monitoring Board (DSMB). This may be done if the IC considers the project to be ‘high risk’. If such a DSMB is established, we will follow the recommendations of the NIH appointed DSMB.

References

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