Yale University Open Data Access (YODA) Project

RESEARCH STUDY PROPOSAL

I. PROJECT TITLE

Title: Meta-analysis of the influence of patient characteristics on the effectiveness and harms of recombinant human bone morphogenetic protein-2 (rhBMP-2) in lumbar spinal fusion.

Description: This study will provide a careful examination on the differences in the effectiveness and harms of rhBMP-2 as compared to iliac crest bone graft (ICBG) in lumbar spinal fusion by patient characteristics. The main patient characteristics will be gender, age, smoking, diabetes status, body mass index (BMI), previous history of back surgery and whether the patients works before surgery. The analysis will be conducted using linear and generalized linear mixed effects model and other patient and study characteristics may be controlled for in the analysis if necessary.

II. PRINCIPAL INVESTIGATOR

Date submitted in Day/Month/Year format: 10/1/2013

Submitting Principal investigator(s): Amber Laurie, MS and Rochelle Fu, PhD

YODA IDs (if applicable):

III. TARGET PUBLICATIONS

☐ Abstract:
Scientific meeting: North American Spine Society
Submission deadline: February 5, 2014
Date of presentation: November 2014, San Francisco

Scientific meeting: International Society for the Study of the Lumbar Spine
Submission deadline: November 15, 2013
Date of presentation: May 2014, Seoul

Scientific meeting: American Association of Neurological Surgeons
Submission deadline: November 4, 2013
Date of presentation: April 2014, San Francisco

Scientific meeting: Congress of Neurological Surgeons
Submission deadline: August 2014
Date of presentation: October 2014, Boston

Scientific meeting: American Academy of Orthopaedic Surgeons
Submission deadline: July 2014
Date of presentation: March 2015, Las Vegas

☐ Manuscript: Target journal(s) (in order of preference):
   1. *Journal of the American Medical Association*
   2. *Spine*
   3. *The Spine Journal*
   Anticipated date of submission: 6/1/2014

IV. BRIEF BACKGROUND/RATIONALE

Two meta-analyses on the use of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) in spine fusion have recently been completed as a result of the Yale University Open Data Access (YODA) Project[1,2]. Both of these reviews used individual-participant data from industry-sponsored, randomized, controlled trials as well as published literature to examine efficacy and safety of rhBMP-2 in comparison to iliac crest bone graft (ICBG). Both reviews found similar results that rhBMP-2 has no or minimal clinical advantage over bone graft and that use of rhBMP-2 may be associated with an increase in risk of some harms[1,2].

However, few studies have focused on the effect of patient characteristics on efficacy and safety. One study comparing rhBMP-2 and ICBG in smokers and non-smokers found that overall smokers had significantly lower fusion rates than non-smokers, but within patients who smoked, those with rhBMP-2 had non-significantly higher fusion rates than those with ICBG[3]. A study in patients over 60 years old found that the use of rhBMP-2 decreased costs and improved outcomes[4], but did not study how age might affect the outcomes.

The current study aims to build on the recent systematic reviews and meta-analyses by focusing on the effect of patient characteristics on effectiveness and harms using individual-patient data from Medtronic's randomized controlled trials in lumbar spinal fusion via the YODA Project. The current study will be the focus of the Master's Thesis in Biostatistics for Amber Laurie, a student at Oregon Health & Science University in Portland, OR.

V. OBJECTIVES

Primary Objective: To determine whether the effectiveness of rhBMP-2 as compared to iliac crest bone graft (ICBG) in lumbar spinal fusion differs by a number of patient characteristics

Secondary Objective: To determine whether the overall harms of rhBMP-2 as compared to iliac crest bone graft (ICBG) in lumbar spinal fusion differs by a number of patient characteristics

VI. STUDY POPULATION

Study Population: All patients included in the Medtronic randomized controlled trials of rhBMP-2 undergoing lumbar spinal fusion for which there is individual patient data (IPD) available for analysis.

Intervention: Fusion using any rhBMP-2 containing intervention
Comparator: Fusion utilizing iliac crest bone graft (ICBG)

VII. Outcomes Measures

Effective Outcomes for Primary Objective
1) Primary: Overall success and spinal fusion
2) Secondary: Patient functional status measured using the Oswestry Disability Index (ODI) and Short Form (36) Health Survey

Harms Outcomes for Secondary Objective
1) Primary: Overall serious adverse events and device-related adverse events
2) Secondary: Overall adverse events

Patient characteristics at Baseline to be Analyzed
1) Age
2) Gender
3) BMI
4) Smoking
5) Presence of diabetes
6) Previous back surgery
7) Preoperative work status

VIII.   DATA ANALYSIS PLAN

Linear and generalized linear models will be used to assess whether the effectiveness and harms of rhBMP-2 will differ by patient characteristics (the one-stage modeling framework[5,6]). Appropriate models will be chosen based on the type of outcomes (continuous or binary). Effectiveness and harms by patient characteristics will be assessed using interaction terms. Surgical approaches, quality of study, worker's compensation and spinal litigation status at baseline will be controlled as a potential confounding variable.

With the benefit of IPD, such analyses examine the differences between patients. However, subgroup analyses are prone to inflated false positive rate[7,8] so this analysis will be limited to the pre-specified variables in section VII. Interpretation of results will carefully consider the consistency among studies and clinical relevance. Randomization of interventions does not stratify by the patient characteristics, therefore the ability to infer causal relationship highly depends on whether the patient characteristics are similar between rhBMP-2 and ICBG within each subgroup and will be examined accordingly.

IX.   REFERENCES

1. Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, Helfand M. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion. *Annals of Internal Medicine.* 2013;158:890-902.
2. Simmonds MC, Brown JVE, Heirs MK, Higgins JPT, Mannion RJ, Rodgers MA, Steward LA. Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion: A Meta-analysis of Individual-Participant Data. *Annals of Internal Medicine*. 2013;158(12):877-889.
3. Glassman SD, Dimar JR, Burkus K, Hardaker JW, Pryor PW, Boden SD, Carreon LY. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. *Spine.* 2007;12:1693-1698.
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6. Turner RM, Omar RZ, Yang M, Goldstein H, Thompson SG. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Statistics in Medicine. 2000;19:3417-32.
7. Yusuf, S., J. Wittes, et al. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *Journal of the American Medical Association.* 1991;266(1):93-8
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