

COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Project Title: Meta-analysis of the Outcomes and Complications in the Spinal Surgery Population Receiving Recombinant Human Bone Morphogenetic Protein-2 vs. Those Receiving Iliac Crest Bone Graft

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I. Hypotheses and Specific Aims:

Hypotheses:

1. Patients exhibiting successful fusion that received recombinant human bone morphogenetic protein-2 (rhBMP-2) had better outcomes and lower complication rates than those receiving iliac crest bone graft (ICBG).
2. Patients exhibiting pseudoarthrosis that received rhBMP-2 had better outcomes and lower complication rates than those receiving ICBG.
3. Patients that received ICBG had an increase in complication rates related to the bone harvest procedure including lasting pain at the site of harvest.

Specific Aims:

1. To retrospectively evaluate the differences in the outcomes and complications in patients that fused with respect to those receiving rhBMP-2 and those receiving iliac crest bone graft.
2. To retrospectively determine the differences in the outcomes and complications in patients that exhibited pseudoarthrosis with respect to those receiving rhBMP-2 and those receiving iliac crest bone graft.
3. To retrospectively determine the complication rates related to the bone graft harvest site in the iliac crest including but not limited to pain, bleeding and infection.

II. Background and Significance:

Spinal arthrodesis (fusion) as a method of surgical stabilization of the spine was introduced in 1911 by Drs. Albee and Hibbs using locally harvested autologous bone for posterior lumbar fusion (PLF)[1]. Subsequently, lumbar vertebral interbody fusion with iliac crest autologous bone graft (ICBG) was applied in the 1930's through anterior (ALIF) or posterior (PLIF) approaches [1-3]

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients suffering from degenerative disc disease[4-6], instability[4] and spondylolisthesis[4, 6]. Because this stabilization procedure does not interfere with the posterior spinal column, it has some advantages to posterior procedures. Using this approach to the lumbosacral spine, the surgeon can expand the disc space and reestablish normal anatomic alignment without injuring the posterior paravertebral muscles. This approach also retains all posterior stabilizing structures and avoids epidural scarring and perineural fibrosis[7]. However, the anterior approach also has significant risks, including damage to abdominal viscera, nerve roots, ureter, and great vessels.

Historically spinal fusions utilize graft material that is harvested from the iliac crest. This method requires an additional surgery that can be the source of complications in its own right [8-15]. More recently the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) has become standard of care in many facilities

including that at the University of Colorado Hospital for lumbar fusion surgeries. Bone morphogenetic proteins (BMPs) are osteoinductive intracellular signaling factors (members of the Transforming Growth Factor β superfamily) that was approved for clinical use by the FDA with corresponding carriers as an alternative to ICBG; rhBMP-2/INFUSE[®] bone graft (Medtronic Sofamor Danek, Memphis, TN) in 2002 [16]. The INFUSE[™] Bone graft/LT-CAGE[™] (rhBMP-2) was approved by the FDA for spinal fusion procedures through an anterior approach (ALIF) in skeletally mature patients with single level degenerative disc disease between L4-S1 [17]. Clinically rhBMP-2 has been utilized not only in the approved ALIF, but also in off-label usage in PLF, TLIF, and cervical cases.

Numerous studies have shown rhBMP-2 as an effective substitute for ICBG, resulting in more rapid and reliable healing [4, 18-26]. However in recent years there have been emerging studies questioning the methodology and adverse event reporting of the initial rhBMP-2 publications [27, 28]. In light of these questions, the Yale University Open Data Access (YODA) project contracted with Medtronic Inc. in order to allow access and reanalysis of all of the clinical trial data with regards to rhBMP-2. The initial systematic review and IDP meta-analysis was undertaken by the Oregon Health and Science University and the University of York. Both studies sought to examine the potential benefits and harms of rhBMP-2 as well as assess the reliability of the published evidence [29, 30]. Fu et al. found that rhBMP-2 and ICBG have similar effectiveness when used in ALIF and PLF and that the risks and occurrences of adverse events were similar. However, this study found substantial evidence of reporting bias in the published articles of the industry sponsored trials [29]. Rodgers et al. found that rhBMP-2 has modest benefits in comparison to ICBG surgeries although adverse events of back and leg pain were more common in patients receiving rhBMP-2. This study also suggests that there were some inconsistencies in the reporting in the publications and that basing any conclusions regarding adverse events from the literature alone would be potentially misleading [30].

Now that the initial studies have been published, YODA is permitting other research groups to apply for access to the information which is the basis for this particular study. The proposed study is novel, as none of the previous studies have specifically divided the groups by those that had successful fusion and those that showed evidence of pseudoarthrosis. In addition the previous works did not single out ICBG complications as a specific aim.

III. Preliminary Studies/Progress Report:

N/A

IV. Research Methods

A. Outcome Measure(s):

Primary and Secondary Outcomes

The primary and secondary outcomes will be evaluated through a review of the neurological function, ODI, SF-36, back pain, leg pain, hip pain, work status and patient reported satisfaction. Complications and adverse events will also be reviewed. The aforementioned measures will be categorized by fused and those exhibiting pseudoarthrosis, with both being subcategorized by those receiving rhBMP-2 or ICBG.

Tertiary Outcome

Subjects that received ICBG will be evaluated for hip pain, bleeding, infection, and other complications associated with the bone graft harvest procedure. In addition lasting pain at the site of harvest will be defined as 24 month follow-up.

B. Description of Population to be Enrolled:

This is a retrospective study of an already compiled data base of 17 studies including 12 randomized controlled trials, of rhBMP-2 and ICBG, provided by Medtronic Inc. to the Yale Open Data Access Project. The review will also include evaluation of other clinical trials as well as cohort studies of rhBMP-2. Thus the combined populations enrolled in the original studies will provide the data for this review.

C. Study Design and Research Methods

The YODA project will provide de-identified patient data for the 17 Medtronic funded studies of rhBMP-2. This study will specifically examine the 7 ALIF studies and the 6 PLF studies. Although there are also two ACDF studies and one circumferential PLIF study, the limited data and different approaches result in their exclusion from this study. This retrospective study will consist of a review of these studies dividing the subjects in to two groups, those that fused and those that exhibited pseudoarthrosis. These groups will then be subdivided by those subjects that received rhBMP-2 and those that received ICBG. The differences between the groups will be assessed through the review of neurological function, ODI, SF-36, back pain, leg pain, hip pain, work status and patient reported satisfaction. Complications and adverse events will also be reviewed. Patients that received ICBG will be further reviewed for hip pain, bleeding, infection, and other complications specifically associated with the bone graft harvest procedure. In addition all of the comparisons will take into account age, gender, race, BMI, smoking status, and diabetic status.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

All of the data that will be used in this study has been previously de-identified by Medtronic and was certified as such by an independent 3rd party. The data use agreement required to access the data base additionally forbids any use of data that will result in re-identification of research participants. All data will be transferred via the Yale secure FTP site and all research on this data will be stored on a secure UCD server.

E. Potential Scientific Problems:

We do not anticipate any scientific problems with this retrospective review.

F. Data Analysis Plan:

To assess the treatment effect of continuous variables, the mean difference and standard error between postoperative (at 24 months follow up) and preoperative evaluations will be determined for each study. The treatment effect of binary data will be assessed as a ratio of studied evidence to sample size at follow up. Pooled mean treatment effects with 95% confidence intervals will be calculated for rhBMP-2 and ICBG groups separately. An inverse-variance method will be utilized for combining data across studies. A random effect model will be applied.

Statistical heterogeneity of pooled data will be defined by the χ^2 test (with p value <0.05 representing heterogeneity) and I^2 test with the following interpretation of heterogeneity: < 30% - low; 30% to 60% - moderate, >60% - high. Grouping analysis will be applied to take into consideration the two surgical techniques. Random effect model will be applied for analysis of each group.

A comparative meta-analysis of treatment effects will be performed by defining pooled differences in means (DM) between BMP and ICBG groups with 95% confidence intervals for continuous indices and a risk ratio with 95% confidence intervals for dichotomous indices. To summarize, a data random effect model will be applied.

G. Summarize Knowledge to be Gained:

The results of this study will provide a better understanding of the differences of outcomes and complication rates of between patients that receive rhBMP-2 and ICBG, both in those that exhibited fusion as well as those that exhibited pseudoarthrosis. This study will continue to build on the existing body of evidence of the complications and long-term pain resulting from the harvest procedure necessary for ICBG. These results will provide additional evidence for spine surgeons as they make informed decisions regarding the best methods of lumbar fusion for their patients.

H. References:

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