

Letters to the Editor NEUROSURGICAL FORUM

Mobi-C cervical artificial disc

TO THE EDITOR: I wish to comment on the recent article by Davis et al.¹ (Davis RJ, Nunley PD, Kim KD, et al: Two-level total disc replacement with Mobi-C cervical artificial disc versus anterior discectomy and fusion: a prospective, randomized, controlled multicenter clinical trial with 4-year follow-up results. *J Neurosurg Spine* 22:15–25, January 2015). This study is troubling on several accounts.

First, the Disclosure reveals flagrant financial relationships between the authors and LDR Medical. It then clearly states, "LDR contributed to the design and conduct of the study and also provided assistance with analysis of data and manuscript review." The fact that such disclosure is required relates to the truth of inevitable bias when such relationships exist. This bias, even with the best intentions, is simply a function of our human nature and has been well documented psychologically. And it must be understood that the actual revelation of these relationships in a disclosure neither establishes an unbiased publication nor exonerates the authors of conscious or subconscious collusion. The disclosure mandate exists to serve as a warning to the readers, and that warning could not be stronger than in this article. Does not the editorial board of the Journal of Neurosurgery: Spine also review article submissions in this light?

Secondly, this article is an extreme representation of how the hardware industry has "driven" the science of spine care. Enrollment in this study is documented simply as "a diagnosis of degenerative disc disease with radiculopathy or myelopathy at 2 contiguous levels from C-3 to C-7." And there were 330 patients in the study. Yet there is no mention that posterior cervical options were considered or discussed with these patients. Hence, the hardware industry, in effect, has dictated surgical care to this group of patients and has done so by providing direct or indirect financial incentives to the surgeon-authors. Does not the *Journal of Neurosurgery: Spine* editorial board consider the ethical questions of such a study?

It should be remembered that the thrust of total disc replacement (TDR) development was for the prevention or moderation of adjacent-segment disease, created by arthrodesis. Yet it is often forgotten that such arthrodesis (anterior cervical discectomy and fusion [ACDF]) is required only as a response to the potential iatrogenic instability and/or deformation in those cases when the surgeon elects to do root decompression from the anterior approach. Thus the predominance of risks and costs in ACDF for radicular symptoms is not directly related to the treatment of symptomatology but is, in fact, the consequence of not electing to do such decompression posteriorly. And the reason for such anterior approach election often stems from the lack of appropriate training and experience in the posterior procedure, again engendered, in part, by financial realities. The single surgical code 63020 has clearly been overwhelmed by the multi-coded ACDF, which renders thousands of dollars more in remuneration to the surgeon or to his or her institutional department.

So now we have come full circle. The above article in effect proselytizes TDR application in patients with vaguely described indications. It has done so under the guidance and financial assistance of the producer of the product in question. And the science of TDR development has been the consequence of problems (mainly adjacent-segment disease) created by ACDF, a procedure that itself has overwhelmed the posterior approach essentially through economic, nonclinical, mechanisms. Isn't it ironic that the main thrust of TDR surgery—motion preservation—is best achieved by the posterior approach? But alas, there is no money in it.

> Edgar N. Weaver Jr., MD Neurosurgical Center of Southwest Virginia, Roanoke, VA

DISCLOSURE

The author reports no conflict of interest.

Reference

 Davis RJ, Nunley PD, Kim KD, Hisey MS, Jackson RJ, Bae HW, Hoffman GA, et al: Two-level total disc replacement with Mobi-C cervical artificial disc versus anterior discectomy and fusion: a prospective, randomized, controlled multicenter clinical trial with 4-year follow-up results. J Neurosurg Spine 22:15–25, 2015

Response

No response was received from the authors of the original article.

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Smoking status in the ACDF versus 2-level total disc replacement study

TO THE EDITOR: I read with interest the article by Davis et al.1 (Davis RJ, Nunley PD, Kim KD, et al: Twolevel total disc replacement with Mobi-C cervical artificial disc versus anterior discectomy and fusion: a prospective, randomized, controlled multicenter clinical trial with 4-year follow-up results. J Neurosurg Spine 22:15-25, January 2015). The authors are attempting to demonstrate the clinical advantages of total disc replacement (TDR) versus anterior cervical discectomy and fusion (ACDF) at 4 years. They note that the nonfusion rate in the 2-level ACDF cohort at 4 years was 14.8%. This did not include patients who underwent revision for failed surgery at an earlier time point, which implies that the overall nonfusion rate was higher. As I understand it, the success of an ACDF relies on the ability of the adjacent bones to fuse, while the TDR does not. Biological fusion is known to be adversely affected by tobacco use.³ While the authors attempted to note smoking status (100% in both groups with no statistical difference) in the patient demographics (Table 3), they segregated smoking status by < 1 versus >1 pack per day. The exclusion criteria (Table 2) specifically excluded patients who smoke > 1 pack per day, so it is not surprising that 100% of patients in both groups smoked < 1 pack per day, rendering the smoking data in Table 3 useless. Although a recent study has shown that smoking may not adversely affect 1-level ACDF with instrumentation,² the authors of that study-and most surgeons, in generalbelieve that multilevel anterior fusions have a higher risk of nonfusion. The authors may be implying that there is a dose-response relationship between the number of cigarettes smoked and the rate of nonfusion, with 1 pack per day being the cutoff. However, I believe that most surgeons counsel ACDF patients to quit smoking to achieve fusion; they do not ask them to reduce their intake to < 1 pack per day. The study also neglects to mention how many of the patients who failed to have fusion were smokers. There is no mention of alternative nicotine delivery (chew, e-cigarettes, hookahs, patches, and so forth). Without a good idea of how many ACDF patients in this cohort were actually using any tobacco, can we be surprised if TDR, which does not rely on biological fusion to achieve clinical success, comes out superior to ACDF, which does?

Sandeep S. Bhangoo, MD, MS

Neurosurgery of North Iowa, Mason City, IA

DISCLOSURE

The author reports no conflict of interest.

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Shaffrey CI, et al: Does smoking have an impact on fusion rate in single-level anterior cervical discectomy and fusion with allograft and rigid plate fixation? Clinical article. **J Neurosurg Spine 19:**527–531, 2013

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Response

No response was received from the authors of the original article.

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Response to letters regarding Mobi-C cervical artificial disc

TO THE EDITOR: We appreciate the opportunity to respond to the 2 letters^{1,7} (Weaver EN Jr: Mobi-C cervical artificial disc. *J Neurosurg Spine* [epub ahead of print May 22, 2015. DOI: 10.3171/2015.2.SPINE15163]; Bhangoo SS: Smoking status in the ACDF versus 2-level total disc replacement study. *J Neurosurg Spine* [epub ahead of print May 22, 2015. DOI: 10.3171/2015.1.SPINE141334]) published on our article (Davis RJ, Nunley PD, Kim KD, et al: Two-level total disc replacement with Mobi-C cervical artificial disc versus anterior discectomy and fusion: a prospective, randomized, controlled multicenter clinical trial with 4-year follow-up results. *J Neurosurg Spine* 22:15–25, January 2015).

Response to Dr. Weaver

The authors on this paper completed personal financial disclosures as required by the journal. It was disclosed that the Sponsor, LDR Spine USA Inc., funded the Investigational Device Exemption (IDE) trial, results of which were reported in this article. Contrary to Dr. Weaver's assertion, the *JNS: Spine* reviewers and the Editor-in-Chief did question the authors' conflicts of interest (COI). In response to the journal inquiry over COI, we added a paragraph to the manuscript, which included analyses of the outcomes from financially interested sites versus sites with no financial interest as defined by FDA regulations. From page 24 of the original article:

All of the authors participated as investigators in the Mobi-C IDE clinical study. To ensure that any potential conflicts of interest have not affected study outcomes, an analysis was completed at each time point to compare the overall success rates of patients between sites with and without financial interest (as defined by FDA regulation 21CFR54). Additionally, this analysis was reported to the FDA as part of the premarket approval package through the 24-month primary endpoint. At 6, 12, 18, 24, 36, and 48 months, this analysis confirmed that financial interest was not indicative of a better (or worse) outcome for either treatment group (p = 0.3132 at 48 months).⁴

The FDA mandates that a Class III medical device be subjected to a Premarket Approval (PMA) study to establish its safety and effectiveness. The required clinical trial is performed under an IDE study protocol subject to strict FDA regulations for study approval and conduct. The costs for such a clinical trial are tens of millions of dollars, before the device is ever approved for market. Due to the limited funding for spine research available from public entities, including the National Institutes of Health, and the tremendous burden of work associated with performing the trial, it is a rarity for a surgeon or group of surgeons to tackle such an endeavor. This leaves industry sponsors little choice but to fund these studies privately, prompting much debate in the medical community. However, according to a recently published article by Cher and Capobianco,² industry-sponsored studies provide higher levels of evidence than studies with other funding sources. These authors reviewed clinicaltrials.gov for medical device research specifically related to the spine through March 6, 2014. They found 200 spine device trials with 148 being industry funded (74%), 3 federally funded, and 49 funded by academia or other sources. Safety and efficacy was the study purpose for 141 of the 148 industry-funded studies, none (0) of the 3 federally funded studies, and 16 of the 49 other funded studies. Further stratification by types of trials showed that 134 of 200 studies were multicenter studies. Multicenter studies will lead to a higher level of evidence in the findings; of the 134 multicenter studies, 118 were industry funded, 2 were federally funded, and 14 were funded by other sources.

While each of the authors agrees that there is a place for the posterior approach, the control treatment that was selected as the most appropriately matched procedure with the same patient indications and surgical approach as the investigational treatment at study start-up (2005), was anterior cervical discectomy and fusion (ACDF). Therefore, the focus on posterior cervical surgery is outside the scope of this study. It is important to note, however, that each patient reviewed and signed a consent form with their surgeon prior to enrollment in the study. Prior to consent, the surgeon explained all treatment options available to the patient. If a surgeon felt that a patient was better suited for a posterior surgery then that patient would not have been a proper candidate for this study and would not have been offered consent. Patients were selected for the study only after they were determined to qualify based on the entire set of 11 inclusion and 33 exclusion criteria. This was a total of 44 eligibility requirements, not "simply a diagnosis of degenerative disc disease with radiculopathy or myelopathy at 2 contiguous levels from C-3 to C-7." The original article listed only the most relevant criteria for brevity, but the full lists of inclusion and exclusion criteria are shown in the Summary of Safety and Effectiveness posted on the FDA website.5

Finally, as clinicians and scientists, we welcome the opportunity to participate in a prospective, randomized, multicenter study that compares total disc replacement (TDR) to posterior cervical surgery regardless of the funding entity.

Response to Dr. Bhangoo

Although the ACDF non-union rate reported (14.8%)

is higher than most surgeons would report clinically in their own practices, there was a much more rigid set of standards for this IDE study. The predefined criteria for radiographic success for the ACDF group included evidence of bridging bone, < 50% radiolucency lines, and < 2° of angular motion. A failure to achieve all 3 criteria resulted in a radiographic non-union designation. Analysis was conducted by Medical Metrics Inc. (MMI, Houston, Texas), who have performed similar analyses in a number of related IDE studies.

The radiographic non-union rate for ACDF was 14.8% at 4 years, which is comparable to the 1-level ACDF data from the ProDisc-C trial report of 13.1% at 5 years⁸ and the Kineflex-C trial report of 18% at 2 years.³ It is note-worthy that these radiographic non-unions at 4 years are identified from radiographs only. The clinical outcomes (as determined by NDI and VAS scores) of ACDF patients with radiographic non-union were similar to those of ACDF patients with successful fusion.

Dr. Bhangoo is correct to identify the study limitation that the inclusion and exclusion criteria in the protocol did not capture smoking status in a manner that allowed for correlation to clinical outcomes. However, 1 pack or less a day was specifically selected to exclude heavy smokers while still allowing for a "real world" population, because approximately 21% of the US population smoked in 2005.6 Dr. Bhangoo brought up some points worthy of consideration. Although the IDE data for smoking in this article were limited, we decided to review our own medical records (not IDE data) to obtain preoperative smoking status for each patient. While it is part of our normal practice to counsel all smoking patients to quit prior to ACDF surgery, we made no assumptions that they actually did and we reported the patient smoking status from their initial assessment. The data retrieved from our 8 investigational sites include 83.6% of the full study cohort (73 ACDF and 203 TDR patients).

Preoperatively, 15.1% (11/73) of ACDF patients and 18.7% (38/203) of TDR patients smoked. ACDF smokers on average smoked 10.3 cigarettes/day and TDR smokers smoked 14.5 cigarettes/day. Comparison of non-union rates for the smokers and non-smokers in the ACDF group for whom 48-month radiographs were available showed that the radiographic non-union rate was significantly higher for patients who smoked (44.4% vs 6.4%, p = 0.0094). When patients who underwent reoperation due to symptomatic non-union are added to the ACDF radiographic non-union rate, patients who smoked had an overall nonunion rate of 70%, compared with the non-smokers' overall non-union rate of 10.6% (p = 0.0003). Clinical outcomes were analyzed between the smoking and non-smoking ACDF patients, including NDI, VAS for neck pain, SF-12 MCS, and SF-12 PCS. For all clinical outcomes there was a statistically significant difference between the 2 groups, with the non-smokers faring better than smokers.

Since this analysis indicated that smoking did impact ACDF fusion and clinical outcomes, we removed all patients who smoked and ran a post hoc comparison of non-smoking ACDF (n = 62) and non-smoking TDR (n = 165) patients. The ACDF non-smoking group experienced less improvement in NDI, VAS Neck, VAS Arm, SF-12 MCS,

and SF-12 PCS than the TDR non-smokers. The IDE study definition of overall success was applied, and 69.8% of the TDR non-smokers met the criteria while only 50.0% of the ACDF non-smokers met the criteria (p = 0.0075).

We thank Dr. Bhangoo and *JNS: Spine* for this opportunity to respond and to provide post hoc analysis. Over the past 10 years, the spine community has been presented with a growing volume of short- and long-term data from a number of IDE clinical studies. We agree with Dr. Bhangoo that our study is not without limitations, and we look forward to eliciting more details on specific long-term treatment effects, including the effect that smoking may have in this patient population.

> Pierce D. Nunley, MD Marcus B. Stone, PhD Spine Institute of Louisiana, Shreveport, LA

> > Michael S. Hisey, MD

Texas Back Institute, Plano, TX

Kee D. Kim, MD

University of California, Davis, Sacramento, CA

Robert J. Jackson, MD Orange County Neurosurgical Associates, Laguna Hills, CA

> Hyun W. Bae, MD Cedars-Sinai Spine Center, Los Angeles, CA

Gregory A. Hoffman, MD Orthopaedics Northeast, Fort Wayne, IN

Steven E. Gaede, MD Oklahoma Brain and Spine Institute, Tulsa, OK

Guy O. Danielson III, MD

Charles Gordon, MD Precision Spine Care, Tyler, TX

Reginald J. Davis, MD

Bimal Rami, MD Greater Baltimore Neurosurgical Associates, Baltimore, MD

DISCLOSURES

LDR contributed to the design and conduct of the study and also provided assistance with analysis of data. Dr. Davis has served as a consultant for LDR, has received clinical or research support for this study from LDR, and has received support for statistical analysis and for study/writing or editorial assistance on this paper from LDR. Dr. Bae is a patent holder for LDR Spine, has invested in a private fund that holds equity in LDR Spine among other medical companies, has received research support from LDR Spine, has served as a consultant for LDR Spine, and receives royalties for products from NuVasive, Stryker, and Zimmer Spine. Dr. Hisey serves as a consultant for LDR Spine, Zimmer Spine, DePuy/Synthes Spine, and Baxano Surgical and is a patent holder for LDR Spine and Zimmer Spine. Dr. Kim is a patent holder for LDR; is a consultant for LDR, Globus, and Stryker; owns stock in Molecular Matrix, Inc; is a consultant for FzioMed; and has a speaking/teaching arrangement with Precision Spine, LDR, and Globus. Dr. Nunley has direct stock ownership in Amedica, Paradigm Spine, and Spineology; has received support of non-study-related clinical or research effort from the Cervical Spine Research Society, K2M, Biomet Spine, Axiomed, Medtronic, Nutech, NuVasive, Spinal Motion, and Vertiflex; has received study related research support from LDR; is a patent holder for K2M and LDR Spine (specifically for the ROI-A anterior lumbar interbody fusion cage); is a consultant for Nutech, Amedica, K2M, and LDR; and has received royalties from, performed speaking and teaching arrangements for, and served on the scientific advisory board of Osprey Biomedical and K2M. Dr. Hoffman has direct stock ownership in, and serves as a consultant to, LDR and Nanovis. Dr. Gaede received clinical or research support for this study from LDR. Dr. Danielson and Dr. Gordon have

received clinical or research support for this study from LDR and are patent holders with LDR (specifically for the ROI-A anterior lumbar interbody fusion cage). Dr. Jackson is a consultant for LDR Spine and has received clinical or research support for this study from LDR. Dr. Stone did not receive research support from LDR for this paper but has received institutional support for the clinical trial and other related research. Dr. Rami has received clinical or research support for this study from LDR.

Dr. Rami has replaced Dr. Davis as the principal investigator on the Mobi-C study at the Greater Baltimore Neurosurgery Center and was involved in formulating this response to the letters by Drs. Weaver and Bhangoo. He is thus included in the authorship despite not having been an author of the original article.

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Modified Bohlman technique

TO THE EDITOR: We read the article by Hire et al.² with interest (Hire JM, Jacobs JM, Bundy JV, et al: A modified Bohlman technique using a novel implant for treatment of high-grade spondylolisthesis. *J Neurosurg Spine* 22:80–83, January 2015).

We would like to draw your attention to our report in which we described a very similar technique that differs from yours only in the fact that we use a titanium transsacral screw instead of an AxiaLif bolt.¹ Moreover, your paper is a case report, whereas our article described a series of 15 patients treated with one-stage posterior decompression stabilization after partial reduction and transsacral interbody fusion. We have now extended our experience to more than 50 patients. Even the chosen levels of arthrodesis you have reported are very similar to ours. We regret that, in your literature review, you were unable to find and make reference to our work on this topic.

Marco Scaglia, MD Marco Andrea Marino, MD Davide Pasquetto, MD Bruno Magnan, MD Integrated University Hospital, Verona, Italy Pietro Bartolozzi, MD

University of Verona, Verona, Italy

DISCLOSURES

The authors report no conflict of interest.

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Response

We thank the authors of the referenced study¹ for reviewing our article and taking the time to send a letter to the editor to encourage discussion on this topic. It is our deficiency for not including your article in our case presentation. A modified Bohlman technique substituting modern implants in lieu of fibular strut autograft is becoming better described, with positive long-term clinical outcomes. The case series presented by Bartolozzi et al. provides an excellent study using a transsacral titanium cage filled with autograft bone graft placed from posterior to anterior across the L5–S1 intervertebral space. The authors describe 15 patients with overall extremely or reasonably satisfactory outcomes per the modified Scoliosis Research Society Outcome Instrument at an average of 31.4 months of follow-up.

The concept of an all-posterior approach in a singlestage surgery with a novel implant is similar to our study, with some differences. The transsacral titanium cage is 7 mm in diameter with a 1-mm thread, with the authors recommending use of an external plastic lumbar support after surgery. The larger, cannulated AxiaLif bolt used in our case presentation has a larger diameter, at 9 or 10 mm, and requires no external support after surgery. Both constructs recommend posterolateral intertransverse fusion with the addition of pedicle screws, most often from L-4 to S-1. Each study agrees with intraoperative partial reduction of the lumbosacral kyphosis associated with high-grade spondylolisthesis. The method of reduction in our case report is via patient positioning with the abdomen hanging unobstructed, which requires less surgical dissection than the proposed method of temporary distraction with Harrington rods between L-2 to the sacral alae and with use of alar staples suggested by Bartolozzi et al. Both techniques are useful for treatment of this disease pathology, describe successful radiographic fusion, and have positive clinical outcomes.

> Justin M. Hire, MD Jeremy M. Jacobs, MD Dwight D. Eisenhower Army Medical Center, Fort Gordon, GA

wight D. Eisenhower Army Medical Center, Fort Gordon, GA

Justin V. Bundy, MD Doctors Hospital, Augusta Orthopedic & Sports Medicine Specialists, Augusta, GA

John G. DeVine, MD

Georgia Regents University, Augusta Hospital System, Augusta, GA

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