Retrograde ejaculation following single-level anterior lumbar surgery with or without recombinant human bone morphogenetic protein–2 in 5 randomized controlled trials

Clinical article

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Object. The aim of this study was to determine the incidence and assess specific risk factors in the postoperative development of retrograde ejaculation (RE) in men treated for degenerative lumbar disc disease at the L4–5 or L5–S1 level with stand-alone anterior interbody implants with or without recombinant human bone morphogenetic protein–2 (rhBMP-2).

Methods. Patients enrolled in 5 prospective, randomized, multicenter FDA-approved investigational device exemption studies were observed for a minimum of 2 years to assess the rate of RE. Five hundred eight men with symptomatic single-level lumbar degenerative disc disease with up to Grade 1 spondylolisthesis underwent anterior lumbar interbody surgery with stand-alone anterior implants at either L4–5 or L5–S1. All patient self-reported and physician-documented adverse events were recorded over the entire course of follow-up. In the investigational groups, 207 patients were treated with an open surgical procedure using dual paired constructs and rhBMP-2 on an absorbable collagen sponge. The control groups (n = 301) were treated with lumbar fusion cage implants and iliac crest autograft or a metal-on-metal disc arthroplasty device. Multivariate analyses of RE were performed to assess the influence of treatment (rhBMP-2), surgical approach, and treated level. Data were analyzed for each trial individually and for the data pooled from the 5 trials.

Results. Retrograde ejaculation occurred at the highest rates in the earliest clinical trial. Of the 146 men, 6 (4.1%) developed RE postoperatively. In subsequent studies, the rates of RE ranged from 0% to 2.1%. Combining the data from the 5 trials, RE was reported in 7 (3.4%) of the 207 patients who received the rhBMP-2 treatment compared with 5 (1.7%) of the 301 patients who received the autograft or lumbar disc treatment (p = 0.242, Fisher exact test). Cases of RE were reported in 7 (1.6%) of 445 patients who underwent a retroperitoneal spinal exposure; 5 RE cases were reported in 58 patients (8.6%) who underwent a transperitoneal approach. The difference in surgical approaches was significant (p = 0.007, Fisher exact test). There was no difference in the rate of RE based on the lumbar level exposed (p = 0.739). Multivariate analyses were consistent with the conclusions from Fisher exact tests. In the initial rhBMP-2 trial, after adjusting for effects of surgical approach and treated level, the difference in RE between the treatment groups (rhBMP-2 vs autograft or disc arthroplasty) was not significant (p = 0.177), however, the difference in RE between the retroperitoneal and transperitoneal approaches was significant (p = 0.029).

Conclusions. In these 5 prospective randomized trials involving anterior lumbar interbody surgery, the use of rhBMP-2 was associated with a higher incidence of RE (3.4% vs 1.7%) but did not reach statistical significance. Based on surgical approach, the difference in rates of RE was statistically significant. This study reports on the outcomes of 5 prospective randomized FDA-approved investigational device exemption trials. Registration for studies became law in 2007. Four of these trials were completed before the law went into effect. The registration number for the lumbar disc arthroplasty trial is NCT00635843.

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Key Words • anterior lumbar interbody fusion • functional neurosurgery • recombinant human bone morphogenetic protein–2 • retrograde ejaculation

IN a prospective RCT published in 2002, investigators found a trend toward a higher rate of RE in patients treated with rhBMP-2 than in those treated with ICBG; however, the difference was not statistically significant.3,19 We undertook a combined analysis to determine if this trend is apparent in other RCTs involving anterior lumbar surgery.

In male patients, RE is a potential complication of ALIF.2,5,10,11,16,20 Infertility can result from the man’s inability to deliver an adequate quantity of spermatozoa to allow fertilization. The reported incidence of RE after ALIF varies widely in the literature. Authors have proposed various factors related to an increased risk of
Retrograde ejaculation after ALIF surgery

RE that include the use of rhBMP-2,10 the interbody implant used,19 surgical approach,11,13,19 surgical technique (use of monopolar electrocautery),18 and surgeon experience.17 Plausible causes include direct injury to a nerve and inflammation. After spinal surgery, the duration of symptoms (transient or permanent) associated with RE and its impact on fertility rates have also not been widely reported or studied. The specific effect of rhBMP-2 on RE rates in men who have undergone ALIF surgery has been reported in only one prospective, controlled, Level I series.5,9 This prospective RCT demonstrated a higher rate of RE in patients treated with rhBMP-2 than in those treated with ICBG; however, this difference was not statistically significant. It is important to note that this study was underpowered to determine if there was a significantly increased incidence of RE with rhBMP-2.

This combined analysis was undertaken to determine if this trend in patients treated using BMP appears in other RCTs involving patients undergoing anterior lumbar spinal surgery. Data from 5 studies were pooled in an attempt to increase the power of the analysis and to potentially identify statistical significance. A meta-analysis of these 5 studies would have been a more conservative analysis (based on repeated testing) and as such was less likely to find a difference between the groups treated with or without rhBMP-2. We analyzed the incidence of RE after interbody surgery among groups treated with rhBMP-2, ICBG, or a lumbar arthroplasty implant. We also compared the incidence of RE in patients who underwent anterior lumbar surgery through a transperitoneal approach with that in those who underwent the surgery through a retroperitoneal approach, and we compared these findings with the incidence of RE reported in other contemporary RCTs.

Methods

Study Design

This study reports on the outcomes of 5 prospective randomized FDA-approved IDE trials. Registration for studies became law in 2007. Four of these trials were completed before the law went into effect. The registration number for the lumbar disc arthroplasty trial is NCT00635843.

Five prospective, randomized, multicenter FDA-approved IDE studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted using a similar fusion technique through 2 different surgical approaches.5,7,12 Institutional review board approval was completed at all study sites, and informed consent was obtained for all patients enrolled in the follow-up studies. According to the protocol designed in partnership with the FDA, all adverse events were collected, regardless of their severity or their relationship to the study treatments.

Between 1998 and 2004, all patients were enrolled in these 5 prospective FDA-approved IDE clinical studies to evaluate the clinical outcomes of a stand-alone ALIF procedure or lumbar disc arthroplasty. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low-back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments.

In these studies, a stand-alone interbody arthrodesis was performed using 3 similar intradiscal implants: 1) threaded, tapered titanium cages (LT-CAGE, Medtronic Spinal & Biologics); 2) threaded, cylindrical allograft bone dowels (MD-IH, Regeneration Technologies, Inc.); and 3) threaded, cylindrical titanium cages (INTER FIX, Medtronic Spinal & Biologics). In 3 studies, enrolled patients were randomized into either the investigational rhBMP-2 group or the control group who received autograft harvested from the iliac crest.5,7,8 In one study, patients were randomly assigned to receive either an interbody fusion or a metal-on-metal disc arthroplasty.12 In these interbody studies, the same concentration of rhBMP-2 and carrier was used.5,7,8 The total dose of rhBMP-2 that the individual patient received varied from 4.2 to 12 mg and depended on the size of the implant used.

Inclusion and Exclusion Criteria

These studies used similar inclusion and exclusion criteria.5,7,8,12 At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4–5 or L5–S1 levels (Table 1). All had had low-back pain for at least 6 months before surgery that was refractory to nonoperative treatment modalities, such as physical therapy, bed rest, and antiinflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone ALIF. Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolysis. Other exclusion criteria were symptomatic disc disease at a level other than L4–5 or L5–S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or nonsteroidal antiinflammatory medications that could interfere with fusion.

**TABLE 1: Patient inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>age ≥18 yrs old</td>
<td>spinal conditions other than DDD</td>
</tr>
<tr>
<td>1-level symptomatic DDD</td>
<td>DDD at disc space levels other</td>
</tr>
<tr>
<td>≤ Grade 1 spondylolisthesis</td>
<td>than L4–5 or L5–S1</td>
</tr>
<tr>
<td>disabling back pain &amp;/or leg pain for &gt;6 mos unresolved by nonoperative treatment</td>
<td>previous anterior fusion at involved level</td>
</tr>
<tr>
<td>additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography</td>
<td>obesity (≥40% above ideal weight)</td>
</tr>
</tbody>
</table>

* DDD = degenerative disc disease; NSAID = nonsteroidal antiinflammatory drug.
Patient Demographics

Our study reviewed only the male patients entered in these 5 clinical studies. The 2 treatment groups were very similar demographically, and there were no statistically significant differences (p < 0.05) for any of the variables.

Study Sites

Combined, patients from 72 study sites were enrolled in these 5 trials, although some study sites participated in one or more of the trials.

Surgical Technique

All patients underwent anterior lumbar spinal exposure through an open approach; there were no laparoscopic surgeries. All surgeries were performed at either the L4–5 or L5–S1 level. The majority of the surgeries were performed using either a retroperitoneal or transperitoneal approach; 5 surgeries in the threaded allograft bone dowel group could not be classified as either transperitoneal or retroperitoneal and therefore were classified as “other.” In the combined trials, there were 3 patients who were treated at the L5–6 level; for analysis, these patients were included in the L5–S1 group. There were no training cases in any of these clinical trials.

Clinical Outcome Measurements

Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Assessment of a patient’s clinical outcome was based on written self-administered patient questionnaires and physical examinations. Data acquisition did not differ among the studies. As a part of the consent process for inclusion in each study, RE was included as a specific risk of the investigational and control surgical procedures in the FDA- and institutional review board–approved written informed consent forms. All participating male patients read a description of RE and indicated by signing the document that they understood the risks described within the consent forms required for inclusion in the studies. At each postoperative follow-up interval, patients were queried regarding adverse outcomes. Patients were not specifically asked about symptoms of RE or any other specific symptom. If a male patient reported RE, an adverse event form was completed, and he was questioned at all subsequent time periods to determine if the condition persisted or had resolved. The rate of patient return for follow-up was high at all postoperative periods in all studies, and there were no marked differences in the overall rates of follow-up, individual or cumulative, in any of the treatment arms. This high follow-up rate enhances the assessment of transient versus permanent RE symptoms.

The study protocol, including the contents of the informed consent form, the methodology for clinical outcomes data collection, and adverse event reporting, was designed in collaboration with the FDA and was monitored by the study sponsor and by the FDA. The data set provided to the FDA and the data reported in the study are identical; there are no known RE events for male patients that were reported by the study sponsor to the FDA that are not included in this paper.

Five Prospective Randomized Clinical Trials

Table 2 summarizes these 5 clinical trials.

Threaded Tapered Titanium Device With rhBMP-2/ACS and ICBG as Control. Between 1998 and 1999, a prospective, randomized, multicenter trial of 279 patients was conducted using the LT-CAGE and rhBMP-2 on an ACS carrier (rhBMP-2/ACS) (INFUSE Bone Graft, Medtronic Spinal & Biologics) as the investigational treatment. All patients underwent a single-level anterior lumbar surgery with the LT-CAGE device (Medtronic Spinal & Biologics). Patients were randomly assigned in a 1-to-1 manner to 1 of 2 groups: the investigational group received rhBMP-2/ACS and the control group received autogenous ICBG. There were no differences between the demographic profiles of the 2 patient populations.

The investigational group (143 patients) received rhBMP-2/ACS; 78 (55%) of the 143 patients were men. Similarly, in the autograft control group, 68 (50%) of the 136 patients were men. A retroperitoneal exposure was carried out in 116 (79%) of these 146 men, and a transperitoneal exposure was used in 30 (21%) of the 146 patients.

Threaded Allograft Bone Dowels With rhBMP-2/ACS and ICBG as Control. Between 1998 and 2001, 2 prospective, randomized, multicenter trials with a total of 131 patients with single-level degenerative lumbar disc disease were conducted. The 2 trials were similar in the pilot and pivotal phases. These 2 sequential prospective FDA-approved IDE clinical trials were conducted to evaluate clinical outcomes of a stand-alone ALIF procedure using dual, paired, threaded cortical allograft dowels. In the pilot phase, 46 patients were enrolled at 5 clinical sites and were randomized using a 1-to-1 ratio. In the pivotal phase, 85 patients were enrolled at 13 clinical sites using a 2-to-1 randomization ratio (2 rhBMP-2/1 ICBG). Between the investigational and control groups, the study protocols for both phases were identical.

All patients underwent single-level stand-alone ALIF surgery with a pair of threaded cortical bone dowels. The patients in the investigational group received rhBMP-2/ACS; in the control group, autogenous iliac crest bone graft was harvested and used in conjunction with the allograft implants. There were no differences between the demographic profiles of the 2 patient populations.

Thirty-two men received the rhBMP-2/ACS treatment, and 19 men received autograft. In this group, 4 transperitoneal surgeries and 42 retroperitoneal surgeries were performed. Five surgeries could not be classified as either transperitoneal or retroperitoneal and were therefore classified as “other.”

Threaded Cylindrical Cage With rhBMP-2/ACS and ICBG as Control. Between 1999 and 2000, in this prospective IDE clinical study, 45 patients underwent anterior lumbar interbody fusion using 2 paired cylindrical threaded titanium fusion cages (INTER FIX). This study used a 1-to-1 randomization ratio of investigational rhBMP-2/ACS (25 patients) to control ICBG (20 patients).

Eleven men received the rhBMP-2/ACS treatment...
and 9 received autograft. In this group, all exposures were performed using a retroperitoneal approach.

**Threaded Tapered Titanium Device With rhBMP-2/ACS as Control and TDR as Investigational Device.** Between 2003 and 2004, a prospective, randomized, multicenter trial of 577 patients was conducted using the LT-CAGE and rhBMP-2/ACS as the control treatment. A metal-on-metal lumbar arthroplasty device (MAVERICK Disc, Medtronic Spinal and Biologics) was used as the investigational device. This study used a 2-to-1 randomization ratio of investigational TDR (405 patients) to control rhBMP-2/ACS patients (172 patients). Seventy investigators and coinvestigators from 31 sites performed surgeries in this clinical study. Eighty-six male patients received the rhBMP-2/ACS treatment, and 205 received the lumbar disc treatment. In this group of male patients, 24 underwent transperitoneal surgeries and 267 underwent retroperitoneal surgeries.

**Statistical Analysis**

For the combined analysis, data from the 5 individual trials were pooled, and standard statistical techniques applied. The Fisher exact test was used to assess all group differences. The approach of pooling the data was used because it was considered a more sensitive approach. As opposed to a meta-analysis, this method of pooling data and analysis enables smaller differences in RE incidence to elicit a statistical difference. A meta-analysis based on repeated testing was not performed because it is less likely to find a difference between the treatment groups. A multivariate analysis of RE was performed by using logistic regression to include the factors of treatment.

**Results**

**Threaded Tapered Titanium Device With rhBMP-2/ACS and ICBG as Control**

Of the 146 men in this prospective study, 6 developed RE. Five of the 6 cases occurred in the rhBMP-2 group, and the other case occurred in a patient who received autograft ICBG. The rates for this adverse event were 5 (6.4%) of 78 in the rhBMP-2 group and 1 (1.5%) of 68 in the ICBG group (Table 2). On the basis of treatment, these rates were not significantly different (p = 0.216, Fisher exact test).

By assessing the surgical approach to the lumbosacral spine and the development of RE, 2 (1.7%) of 116 men in the retroperitoneal approach group and 4 (13.3%) of 30 men in the transperitoneal group reported this complication. On the basis of treatment, this difference in the surgical approach is statistically significant (p = 0.017, Fisher exact test). In this study, patients who underwent anterior lumbar disectomy and interbody fusion through a transperitoneal approach to the lumbar spine at L4–5 and L5–S1 had a 10 times higher incidence of RE than patients who underwent lumbar fusion through a retroperitoneal approach.

Multivariate analyses of RE were performed using a logistic regression that included treatment (rhBMP-2 or autograft), surgical approach, and treated level. Consistent with the conclusions from the Fisher exact tests, after adjusting for effects of surgical approach and treated level, the difference in RE was not significant (p = 0.177) between the rhBMP-2 and autograft treatment groups (Table 3). Meanwhile, independent of treatment and the treated level, the difference in RE between the retroperitoneal and transperitoneal approaches was significant (p = 0.029).

The condition of 3 of the 6 men with RE in this study resolved. At 1-year postoperatively, the symptoms were resolved in one man in the rhBMP-2 group and another in the autograft group, and at 48 months after surgery, a second patient in the rhBMP-2 group had resolution of his symptoms of RE. At the last clinical follow-up examination, the final rate for RE in the rhBMP-2 group was 3.8% (3 of 78).

**Threaded Allograft Bone Dowels With rhBMP-2/ACS and ICBG as Control**

None of the 51 men treated with rhBMP-2 or autograft in either the pilot or pivotal clinical trials reported RE.
TABLE 3: Multivariate analyses of RE using treatment (rhBMP-2 or autograft), surgical approach, and treated level

<table>
<thead>
<tr>
<th>Study</th>
<th>Factors</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhBMP-2/LT-CAGE</td>
<td>treatment (rhBMP-2 vs non–rhBMP-2)</td>
<td>0.177</td>
</tr>
<tr>
<td></td>
<td>surgical approach (retroperitoneal vs transperitoneal)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>treated level (L4–5 vs L5–S1)</td>
<td>0.538</td>
</tr>
<tr>
<td>lumbar arthroplasty</td>
<td>treatment (rhBMP-2 vs non–rhBMP-2)</td>
<td>0.825</td>
</tr>
<tr>
<td></td>
<td>surgical approach (retroperitoneal vs transperitoneal)</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td>treated level (L4–5 vs L5–S1)</td>
<td>0.623</td>
</tr>
<tr>
<td>pooled data</td>
<td>treatment (rhBMP-2 vs non–rhBMP-2)</td>
<td>0.423</td>
</tr>
<tr>
<td></td>
<td>surgical approach (retroperitoneal vs transperitoneal)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>treated level (L4–5 vs L5–S1)</td>
<td>0.727</td>
</tr>
</tbody>
</table>

Threaded Cylindrical Cage With rhBMP-2/ACS and ICBG as Control

None of the 20 men treated with rhBMP-2 or autograft in this study reported RE.3,4

Threaded Tapered Titanium Device With rhBMP-2/ACS as Control and TDR as Investigational Device

In this second RCT using paired LT-CAGE implants, the rhBMP-2/ACS treatment via an open anterior interbody procedure was used as the control and an artificial lumbar disc was the investigational device.12

Retrograde ejaculation was reported in 2 (2.3%) of the 86 men who received the rhBMP-2 treatment compared with 4 (2.0%) in the 205 men who received the lumbar disc treatment. The rates were similar (p = 1.000, Fisher exact test) between the 2 treatment groups. Among the 6 RE cases, 1 (4.2%) was among the 24 surgeries using the transperitoneal approach, while the other 5 (19.0%) were among the 267 surgeries using the retroperitoneal approach. The difference was not significant (p = 0.406).

Multivariate analyses of RE assessing the effect of treatment (rhBMP-2 or not), surgical approach, and treated level showed that none of these factors were significant (p values of 0.825, 0.442, and 0.623, respectively).

Clinical follow-up of the 6 patients who developed RE postoperatively showed that the symptoms resolved spontaneously in 4. All patients treated with rhBMP-2 had resolution of their symptoms by 6 months after surgery. Two of 4 patients treated with disc replacement had resolution of their RE symptoms at 12 and 24 months after surgery.

Combined rhBMP-2/ACS Study Outcomes

Combining the data from all 5 trials, RE was reported in 7 (3.4%) of the 207 men who received the rhBMP-2 treatment compared with 5 (17%) of the 301 men who received the autograft or lumbar disc treatment (p = 0.242, Fisher exact test) (Table 4). A total of 12 RE events were recorded in 508 patients. The null hypothesis is that the 2 cohorts are the same, and we can assume that rate to be 2.36%. A reasonable risk increase that one wants to detect is probably 2 times, that is, 4.72%. With those assumptions, it would give a power of 23% (Fisher exact test). When the surgical approach was compared, 7 RE cases (1.6%) were reported in the 445 men who underwent a retroperitoneal surgical exposure of the lumbosacral spine, and 5 cases (8.6%) in the 58 men who had surgery via a transperitoneal exposure reported RE. The difference was significant (p = 0.007, Fisher exact test).

The lumbosacral level approached surgically (L4–5 vs L5–S1) was not associated with the development of RE (Table 5). The L4–5 level was approached in 127 male patients. Retrograde ejaculation developed postoperatively in 2 (1.6%) of these patients. The L5–S1 level was approached in 381 male patients, including the 3 patients treated at the L5–6 level who were included in the lumbosacral study for analysis. Retrograde ejaculation developed postoperatively in 10 patients (2.6%). The difference between surgical levels was not statistically significant (p = 0.739).

Retrograde ejaculation occurred at the highest rates in the earliest clinical trial that began enrolling patients in 1998. Six (4.1%) of 146 men developed RE postoperatively. In subsequent studies, the rates of RE ranged from 0% to 2.1%.

Multivariate analyses of RE were performed using logistic regression that included the factors of treatment (rhBMP-2 or no rhBMP-2), surgical approach, and treated level from the pooled data from the 5 trials. Consistent with the conclusions from the Fisher exact tests from each individual clinical trial, the difference in RE was not significant (p = 0.423) between the treatment groups (rhBMP-2 or no rhBMP-2), independent of surgical approach and treated level. Again, the treated level did not significantly affect the RE rates (p = 0.727). Importantly, the difference in RE was highly significant (p = 0.004) between the retroperitoneal and transperitoneal approaches after adjusting for effects of treatment and treated level.

Discussion

In previous publications, RE was reported as an adverse event in the pivotal, prospective, randomized, controlled study investigation of INFUSE Bone Graft in ALIF with an LT-CAGE device; however, the rate of RE was reported by surgical approach rather than by treatment.5,19 Recently, questions have been raised regarding the potential role of rhBMP-2 in the incidence of RE13,21,22 The rates by treatment group demonstrated a 5 times higher rate in patients treated with rhBMP-2 (6.4%) than in those treated with ICBG (1.5%). Although this trend was not statistically significant in the 2 groups, further analysis was warranted to determine clinical significance of this trend. The purpose of this study was to determine if this trend was observed in other prospective RCTs utilizing rhBMP-2 in ALIF procedures. A higher rate of RE in patients treated with rhBMP-2 was not reproduced in any of the 4 other sequential trials.7,8,15 In 3 of these trials, no patient reported RE. In the remaining trial randomizing TDR versus ALIF surgery with dual cages and rhBMP-2, 6 (2.1%) of 291 patients...
reported RE. Two (2.3%) of 86 cases occurred in the rhBMP-2 group and 4 (2.0%) of 205 cases occurred in the TDR group. The trial with the highest rate of RE was the first of the 5 trials completed. This higher rate of RE may represent limited surgical experience with the demanding surgical technique required for the insertion of 2 paired threaded cages. Several authors have proposed that the use of threaded interbody fusion cages is associated with various risks, including an increased chance of RE. The placement of impacted nonthreaded devices during ALIF was associated with lower rates of RE.

A limitation of all of these studies concerns data acquisition. Before surgery, all male patients who enrolled in these studies were made aware of the risks of RE. After surgery, patients self-reported any adverse events; however, male patients were not questioned specifically regarding sexual function. It is possible that the rates of RE were underreported. This analysis compares the between-group differences; it does not attempt to provide a rate of RE for anterior surgical populations. Importantly, none of the clinical trials included in this analysis was powered to detect a difference in RE. This pooled analysis presents the differences in RE from spontaneous reporting.

### Threaded Tapered Titanium Device With rhBMP-2/ACS as Control and TDR as Investigational Device

In this second, sequential RCT using the LT-CAGE and rhBMP-2/ACS device, the interbody fusion group was treated through an open anterior interbody procedure and was used as the control group; an artificial lumbar disc was the investigational device. In this study, RE was reported in 2 (2.3%) of the 86 men in the rhBMP-2-treated group, compared with 4 (2.0%) of the 205 men who received the lumbar arthroplasty device. The rates were similar (p = 1.000), which again confirmed no relationship between the use of the rhBMP-2 and RE occurrence. Among those 6 cases of RE in this second study, 1 case (4.2%) was among a total of 24 transperitoneal surgeries, while the other 5 (1.9%) of 267 cases occurred with the retroperitoneal approach. In this individual study, although not reaching statistical significance, the rate of RE was twice that in the transperitoneal group compared with that of the retroperitoneal group.

### Threaded Allograft Bone Dowels and Threaded Cylindrical Cage With rhBMP-2/ACS and ICBG as Control

From the data presented in the rhBMP-2/LT-CAGE open RCT, there were 143 investigational (rhBMP-2) patients and 136 control (ICBG) patients. One hundred forty-six men underwent an open surgical exposure of the lumbosacral junction and a single-level interbody fusion at either the L4–5 or L5–S1 level. Five of the 6 cases of RE occurred in men in the rhBMP-2 group, while the other was in a patient who received autograft ICBG. The rates were 5 (6.4%) of 78 and 1 (1.5%) of 68. These rates do not meet the level of statistical significance and are not considered significantly different on the basis of treatment (p = 0.216, Fisher exact test).

In this study of 146 men, 2 cases of RE occurred in 116 patients who underwent a retroperitoneal surgical exposure (1.7%). Four cases of RE occurred in 30 patients who had a transperitoneal surgical exposure (13.3%). This difference is statistically significant (p = 0.017).
TABLE 5: Retrograde ejaculation events and level of surgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study</th>
<th>L4–5 Level</th>
<th>L5–S1 Level</th>
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<tr>
<td></td>
<td>Retropitoneal</td>
<td>Transperitoneal</td>
<td>Retropitoneal</td>
</tr>
<tr>
<td></td>
<td>rhBMP-2</td>
<td>p Value</td>
<td>rhBMP-2</td>
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<tr>
<td>Burkus et al., 2002 &amp; 2005</td>
<td>rhBMP-2/bone dowel vs autograft</td>
<td>11 2</td>
<td>0 0</td>
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<tr>
<td>no. of men</td>
<td>11</td>
<td>11</td>
<td>11</td>
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<tr>
<td>no. w/ RE (%)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burkus, 2004 &amp; 2005</td>
<td>rhBMP-2/titanium cage vs autograft</td>
<td>1 5</td>
<td>0 0</td>
</tr>
<tr>
<td>no. of men</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>no. w/ RE (%)</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Burkus et al., 2002 &amp; 2005</td>
<td>rhBMP-2/LT cage vs autograft</td>
<td>13 0.613</td>
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<td>no. of men</td>
<td>18</td>
<td>0.613</td>
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<td>no. w/ RE (%)</td>
<td>1</td>
<td>1 (5.5)</td>
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<td>Gornet et al., 2011</td>
<td>rhBMP-2/LT CAGE vs lumbar arthroplasty</td>
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<td>no. of men</td>
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<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>no. w/ RE (%)</td>
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<td>1.000</td>
<td>1.000</td>
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<tr>
<td>total</td>
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<tr>
<td>no. of men</td>
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</tr>
<tr>
<td>no. w/ RE (%)</td>
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Retrograde ejaculation after ALIF surgery

Combined rhBMP-2/ACS Study Outcomes

Combining the data from these sequential studies for a composite analysis is justified due to the large number of similar factors: surgical technique, rhBMP-2 dosing, dual threaded cages, inclusion/exclusion criteria, similar study design (prospective, randomized FDA-regulated trials), and patient demographics.

In the combined data from the 5 studies, RE was reported in 7 (3.4%) of the 207 men who received rhBMP-2 treatment and 5 (1.7%) of the 301 men who received autograft or lumbar disc treatment (p = 0.242). In the combined data from the 5 studies, 7 cases of RE (1.6%) were reported in 445 patients undergoing retroperitoneal approaches and 5 cases of RE (8.6%) cases were reported in a total of 58 patients undergoing transperitoneal approaches. The difference based on surgical approach is significant (p = 0.007). The combined data from these 5 studies show that the lumbosacral level approached surgically (L4–5 vs L5–S1) was not associated with the development of RE.

Transient Versus Permanent RE Condition

The development of RE symptoms after anterior lumbar surgery is not always a permanent condition. In these combined studies, 12 of 508 men developed postoperative RE. These symptoms spontaneously resolved in 7 patients: 4 (57%) of 7 patients in the rhBMP-2-treated group and 3 (60%) of 5 patients in the autograft/disc arthroplasty group.

Contemporary FDA IDE Prospective RCTs Using Dual Interbody Fusion Cages and ICBG

Rates of RE identified in these 5 studies can be compared with similar contemporary studies. Contemporary FDA IDE clinical trials were similarly performed under independent oversight and have similar prospective randomized study designs.

Sasso et al. published results from an FDA IDE prospective RCT comparing a cylindrical threaded titanium cage (INTER FIX) with a femoral ring allograft control for ALIF. An ICBG was used in both patient study groups. Retrograde ejaculation occurred in 6 (7.2%) of the 83 men in the investigational group treated with dual-paired fusion cages; no cases of RE were identified in the 33 men in the femoral ring control group.

Blumenthal et al. conducted an FDA IDE lumbar arthroplasty device study comparing the safety and effectiveness of the CHARITÉ Artificial Disc (DePuy Spine, Inc.) in ALIF surgery using dual-paired interbody cages for the treatment of single-level degenerative disc disease at the L4–5 and L5–S1 levels. Retrograde ejaculation occurred in 3 (5.5%) of the 55 men treated with ICBG and dual fusion cages and in 3 (3.3%) of the 92 men treated with the disc arthroplasty. The rate of 3.3% for RE compares quite similarly with the final rate of 3.8% in the first rhBMP-2 cage study.

Two sequential prospective, multicenter FDA-approved IDE studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar transperitoneal fusion technique through a laparoscopic surgical approach (Table 6). Dual tapered interbody fusion cages were used in both studies. The first study used ICBG exclusively as graft material, and the second study used rhBMP-2/ACS. In the laparoscopic ICBG fusion study group, 23 (16.2%) of 142 men reported RE. In the laparoscopic rhBMP-2/ACS treated group, 6 (10.5%) of 57 men reported RE. The rate of RE reported in these studies was reduced from 16.25% to 10.5% when rhBMP-2 was used by more experienced surgeons.

Contemporary Non-FDA IDE Trials

Lieberman et al. reported results from a prospective clinical trial of the transperitoneal laparoscopic approach to the lumbar spine in a consecutive series of patients undergoing ALIF using dual fusion cages. Retrograde ejaculation has occurred in 2 men (7%).

Escobar et al. conducted a retrospective review involving 135 patients undergoing anterior interbody fusion using 4 different approaches to the lumbosacral spine. Patients were included if either bone grafts alone or cylindrical cages with bone graft inside was used. Patients who had surgery with anterior instrumentation using plates or rods were excluded. Retrograde ejaculation occurred in 4 (8%) of the 50 male patients: 3 (25%) in the transperitoneal video-assisted group and 1 (2%) in the minilaparotomy group.

Smoljanovic et al. speculated that there is a higher rate of RE following ALIF surgery using rhBMP-2. They proposed several different etiologies. Their commentary stimulated Carragee and coworkers to conduct a retrospective review of a cohort of male patients within Dr. Carragee’s practice. The authors reported on 247 nonrandomized retrospectively reviewed male patients who underwent 1- and 2-level ALIF surgeries using various implants, with and without various anterior fixation techniques through 2 different retroperitoneal approaches. They chose from previously reported patient cohorts treated between 2000 and 2004 that included “a mix of cases before and after rhBMP-2 was introduced.” A portion of these patients also underwent various posterior fixation. Previous reports detailed stable and unstable spondylolisthesis. Remarkably, despite using a largely abandoned central surgical exposure to the disc space, they reported no cases of RE in this series of single-level fusions using autograft. They did not report how the appropriate volume of rhBMP-2/ACS used in each case was determined. Based on the findings in this retrospective case review study, Carragee and Wildstein speculated that the use of rhBMP-2 is associated with a higher rate of RE through an unsubstantiated postoperative swelling or inflammatory mechanism.

Surgeon Experience and the Development of RE

In a letter to the editor, Birch and Shaw proposed that RE occurrences highly depend on a surgeon’s experience and surgical technique, as their own experience showed. The risk could be greatly minimized as surgeons become familiar with the surgical technique and gain experience. From a second analysis of CHARITÉ disc replacement
study populations, researchers found that the higher the number of cases an individual surgeon performed and the greater the number of cases performed at an institution, the lower the rate of major complications and neurological deterioration. Similar findings in the ProDisc FDA IDE study show that RE occurred in 2 (10%) of the 20 men included in the initial training cases. The rate of RE decreased to 2.4% (2 of 83 men) in the pivotal portion of the study.

The data from the 5 trials using rhBMP-2/ACS were collected from surgeons who performed the operative procedures without any trial or practice cases. It is not surprising that the first trial had the highest rate of RE. Later trials showed reduced rates of RE, which may, in part, be related to surgeon experience with the approach.

Conclusions

From the pooled data from these 5 prospective RCTs involving anterior lumbar interbody surgery, there was no significant difference in the proportion of men experiencing RE who were treated with rhBMP-2 and those who were not treated with rhBMP-2. Patients in the earliest study treated with rhBMP-2 and threaded fusion cages had the highest rates of RE. These studies confirmed that the use of a transperitoneal approach to the lumbar spine at L4–5 and L5–S1 levels has a 5 times greater chance of causing RE in men than a retroperitoneal approach; this difference in surgical approach reaches the level of statistical significance (p = 0.007) in the development of postoperative RE. The lumbosacral level approached statistical significance (p = 0.007) in the development of postoperative RE. The postoperative development of RE is not statistically significant (p = 0.2807) in the development of postoperative RE. The postoperative development of RE after ALIF surgery resolved spontaneously in more than half of the patients who initially reported symptoms.

These 5 prospective randomized trials demonstrated a higher rate of RE with the use of rhBMP-2 in stand-alone interbody fusion cages; however, this difference was not statistically significant.

In addition, the studies support findings in the literature from contemporary prospective trials that the use of dual paired interbody cages is associated with an increased risk of postoperative RE. Similarly, surgeon technique and experience may be related to the risk of RE. These studies confirm the fact that there is no relationship between the use of rhBMP-2 in stand-alone interbody fusion cages and the postoperative development of RE.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Burkus. Analysis and interpretation of data: all authors. Drafting the article: Burkus. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Burkus. Study supervision: Burkus.

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Retrograde ejaculation after ALIF surgery

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