Safety and Efficacy of Bioabsorbable Cervical Spacers and Low-Dose rhBMP-2 for Multilevel ACDF

Kaveh Khajavi, MD, FACS
Alessandria Struebing, MSPH
Disclosures

- NuVasive, Inc.
  - Consultant

- FDA off-label usage
  - rhBMP-2 (INFUSE, Medtronic Sofamor Danek)

- All products discussed, spacer, infuse, and plate, all sold by Medtronic

- No relationship with Medtronic
Introduction

- Single-level ACDF:
  - high fusion rates, regardless of graft choice or instrumentation

- Multi-level ACDF:
  - variable fusion rates (56-100%)
  - Much higher failure rate, and complication rate
  - highly dependent upon graft choice, interbody spacer, instrumentation, # of levels, host factors, & definition

- Autograft is gold standard, but used less today

- Structural allograft used commonly but may result in lower fusion rates in multilevel cases
Other Spacer and Graft Options

- Synthetic spacers filled with graft material
  - Metal options
  - PEEK: most commonly used
    - Radiolucent
    - Modulus of elasticity similar to bone

- Bioabsorbable Spacer

- Many Graft options exist
  - Local bone
  - DBM
  - Ceramics
  - Tricalcium phosphate

- BMP
Bioabsorbable cervical spacers (BCS)

- Radiolucent; Modulus of elasticity similar to bone
- Rigid during implantation to provide immediate biomechanical stability, steadily degrades over time allowing gradual transfer of stresses to the graft material, degrades completely when fusion matured
- No issues with particulate debris or retained foreign body like PEEK
- The safety of polymers and their degradation products has been adequately demonstrated in the plastic surgery and orthopedic literature (suture, suture anchors, fracture fixation screws, etc.)
• Cornerstone HSR used in this study
  ○ Medtronic Sofamor Danek, Memphis, TN
  ○ Noncrystalline polylactide copolymer of polylactide, 70:30 poly (L-lactide) to poly (D,L-lactide)
  ○ Degraded slowly to lactic acid ➔ pyruvic acid ➔(via Krebs cycle) is excreted as CO2 and water
rhBMP-2

- rhBMP-2 (Infuse, Medtronic Sofamor Danek, Memphis, TN)
  - Achieves fusion at least as well as autograft
  - NOT FDA approved for use in the cervical spine
  - Significant complications have been reported
Methods
Study Overview

- **Study Design**
  - Prospective observational cohort
    - IRB approved, prospective registry (ProSTOS, PhDx)

- **Inclusion Criteria**
  - Consecutive patients treated between 2007-2012 \(n=72\)
  - Multi-level (2+) ACDF with BCS and low-dose rhBMP-2 (& local bone if available)
  - Failure of conservative treatments and available for follow-up
Methods

- 72 patients, 187 levels
  - 37 (51%) 2-level cases
  - 27 (38%) 3-level cases
  - 8 (11%) 4-level cases

- Primary Diagnosis:
  - Spondylosis: 40
  - Deformity/subluxation: 13
  - HNP: 8
  - Non-Union: 7
  - ASD: 4

Most (65%) patients had > 1 primary diagnosis
## Methods

### Patient Samples

<table>
<thead>
<tr>
<th></th>
<th>All (n=72)</th>
<th>2 Levels (n=37)</th>
<th>3+ Levels (n=35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-Up (months) – mean ± SD</strong></td>
<td>13.8 ± 6.8</td>
<td>14.2 ± 7.0</td>
<td>13.3 ± 6.6</td>
<td>0.574</td>
</tr>
<tr>
<td><strong>Age (years) – mean ± SD</strong></td>
<td>55.3 ± 10.4</td>
<td><strong>51.8 ± 9.5</strong></td>
<td>59.0 ± 10.2</td>
<td><strong>0.003</strong>*</td>
</tr>
<tr>
<td><strong>Female – n (%)</strong></td>
<td>51 (70.8)</td>
<td>26 (70.3)</td>
<td>25 (71.4)</td>
<td>0.977</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) – mean ± SD</strong></td>
<td>28.4 ± 5.6</td>
<td>27.9 ± 5.6</td>
<td>28.8 ± 5.7</td>
<td>0.497</td>
</tr>
<tr>
<td><strong>Tobacco Use – n (%)</strong></td>
<td>24 (33.3)</td>
<td><strong>16 (43.2)</strong></td>
<td>8 (22.9)</td>
<td>0.067</td>
</tr>
<tr>
<td><strong>Previous Cervical Surgery – n (%)</strong></td>
<td>12 (16.7)</td>
<td>8 (21.6)</td>
<td>4 (11.4)</td>
<td>0.246</td>
</tr>
</tbody>
</table>
Methods
Surgical Summary

<table>
<thead>
<tr>
<th>Primary Indication – n (%)</th>
<th>All (n=72)</th>
<th>2 Levels (n=37)</th>
<th>3+ Levels (n=35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSM only</td>
<td>29 (40.3)</td>
<td>17 (45.9)</td>
<td>12 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Radiculopathy only</td>
<td>27 (37.5)</td>
<td>14 (37.8)</td>
<td>13 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Both CSM + Radiculopathy</td>
<td>15 (20.8)</td>
<td>6 (16.2)</td>
<td>9 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>rhBMP-2 (mg) – mean ± SD</td>
<td>0.58 ± 0.1</td>
<td>0.58 ± 0.1</td>
<td>0.58 ± 0.1</td>
<td>.0963</td>
</tr>
<tr>
<td>OR Time (min) – mean ± SD</td>
<td>144.4 ± 41.8</td>
<td>123.3 ± 33.0</td>
<td>171.3 ± 36.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>EBL (mL) – mean ± SD</td>
<td>49.0 ± 43.8</td>
<td>52.9 ± 57.0</td>
<td>44.6 ± 20.0</td>
<td>0.502</td>
</tr>
<tr>
<td>LOS (days) – mean ± SD</td>
<td>1.1 ± 0.6</td>
<td>1.2 ± 0.8</td>
<td>1.0 ± 0.0</td>
<td>0.109</td>
</tr>
</tbody>
</table>
Methods

- Clinical Outcomes
  - NDI
  - NRS (neck & arm, 0-10)
  - SF-36 (PCS & MCS)
  - Patient satisfaction

- Imaging Studies
  - Initial x-rays within 24 hours of surgery
  - AP and lateral x-rays at 4-6 weeks
  - Serial x-rays with flexion/extension at 3, 6, 12, 24 months
  - CT obtained only if uncertainty regarding fusion status
Methods

- **Dysphagia Classification**
  - Quantified if symptoms were unresolved by 2 weeks PO or hospital readmission and additional treatment were required
  - “Prolonged” dysphagia: present ≥ 1 month po visit
  - “Persistent” dysphagia: present ≥ 3 month po visit

- **Analysis**
  - Chi-squared/Fishers’ Exact tests and one-way ANOVA
  - Significance accepted for p ≤ 0.05
### Results

#### Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Levels ($n=37$)</th>
<th>3+ Levels ($n=35$)</th>
<th>Total ($n=72$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLL injury • Return to OR for symptomatic nonunion</td>
<td>2 (5.4%)</td>
<td></td>
<td>5 (6.9%)</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD exacerbation • Readmit within 30 days PO for nausea</td>
<td>2 (5.4%)</td>
<td>1 (2.9%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>AFIB exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 pt with symptomatic pseudoarthrosis (1.4%)
Results
Adverse Events: Dysphagia

- 38 patients (53%) had dysphagia that was not resolved by 2 week PO
  - 21 patients had their dysphagia symptoms resolved by 1 month
  - 13 patients had their dysphagia symptoms resolved by 3 months
  - 2 patient had their dysphagia symptoms resolved by 6 months
  - 2 patients had dysphagia 1 & 3 months then no dysphagia data/lost to f/u

- 2 of these patients required readmission and observation/IV steroids
- All resolved by 6 months

Prolonged dysphagia 17/72 = 24%  Persistent dysphagia 4/72 = 6%
<table>
<thead>
<tr>
<th>Levels</th>
<th>Dysphagia</th>
<th>No dysphagia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 levels</td>
<td>18</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>3 levels</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>4 levels</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

P-value = 0.064
Results
Clinical Outcomes: NDI & SF-36 PCS

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>43.6%</td>
<td>46.6%</td>
</tr>
<tr>
<td>2 Levels</td>
<td>40.2%</td>
<td>46.3%</td>
</tr>
<tr>
<td>3+ Levels</td>
<td>21.8%</td>
<td>45.6%</td>
</tr>
</tbody>
</table>

% Improve:
- All Patients: 42.6%
- 2 Levels: 39.1%
- 3+ Levels: 45.7%

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>37.5</td>
<td>46.3</td>
</tr>
<tr>
<td>2 Levels</td>
<td>36.7</td>
<td>45.6</td>
</tr>
<tr>
<td>3+ Levels</td>
<td>38.5</td>
<td>47.0</td>
</tr>
</tbody>
</table>

% Improve:
- All Patients: 23.4%
- 2 Levels: 24.4%
- 3+ Levels: 22.2%
It should be noted that the clinical indication for surgery was myelopathy in 40% of patients in the current series, and thus, the NDI, which contains questions mostly related to disability as a result of radicular symptoms, may not reflect the “true disability” for these patients.
Results
Clinical Outcomes: NRS Neck & Arm

Neck

<table>
<thead>
<tr>
<th></th>
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<th>Last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>5.5</td>
<td>2.2</td>
</tr>
<tr>
<td>2 Levels</td>
<td>5.8</td>
<td>2.5</td>
</tr>
<tr>
<td>3+ Levels</td>
<td>5.2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

% Improve: 60.0%

Arm

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>5.8</td>
<td>2.6</td>
</tr>
<tr>
<td>2 Levels</td>
<td>5.6</td>
<td>3.3</td>
</tr>
<tr>
<td>3+ Levels</td>
<td>6.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

% Improve: 55.2%

All Patients 60.0%
2 Levels 57.7%
3+ Levels 63.6%

All Patients 55.2%
2 Levels 40.5%
3+ Levels 68.3%
Results
Patient Satisfaction

How satisfied are you with your surgical outcome?

- All Patients: 96.9%
- 2 Levels: 100%
- 3+ Levels: 93.5%

Given your current condition, would you elect to have the same surgery again?

- All Patients: 93.9%
- 2 Levels: 93.8%
- 3+ Levels: 92.9%
ACDF x 2 for myelopathy

54 yo M CSM, Rt hemibody N/T 10 mo; inc DTRs, Hoffmans, clonus
ACDF x 2 for cerv radiculopathy

- 71 y/o female
- CC:
  - 3+ years neck pain + left C6 radiculopathy
  - Left 4+/5 deltoid weakness
  - Left 4/5 bicep weakness
  - Left 4-5 BR and WE weakness
- Cervical radiculopathy
  - C4-5 DDD and subluxation
  - C5-6 severe DDD
- C4-6 ACDF
  - BCS
  - 0.5mg rhBMP-2 per level + crushed local autograft
  - C4-6 anterior cervical plating
• Expected dysphagia immediately PO, resolved by 2 weeks PO

• Clinical outcomes (24MO)
  o NDI  52 → 16
  o NRS Neck  8 → 0
  o NRS Arm  6 → 0
  o SF-36 PCS  41.4 → 59.1
  o SF-36 MCS  25.3 → 45.3

• Patient satisfaction
  o Very satisfied with surgical outcome
  o Would definitely do again
ACDF x 2 for pseudo and ASD

45 yo F s/p C5-6 ACDF 2004 , with chronic NP & Left C7 radic
ACDF C45, C6-7
4 years PO
ACDF x 2 for ASD

- 63 y/o female
- PMHx
  - 2 years post C4-6 ACDF with PEEK cages 2009
- Presents 2010 with increasing NP, L shoulder pain
- In 2011 develops Left C7 radic
ACDF x 3 for myelopathy & radiculopathy

79 yo F with CSM & radic
ACDF x 4 for CSM

77 yo F CSM, N/C hands 5 yrs, lermittes, intrinsic hand weakness, hoffmans signs
Immediate PO
Only case of symptomatic non-union

May 2010

May 2011
Felt she had ASD C3-4 and C6-7

C3-4/C6-7 ACDF July 2011

- BCS
- 0.5mg rhBMP-2 per level + crushed local autograft
- Mild, transient prolonged dysphagia resolved by 1MO PO
- 6 MO PO
  - Solid C3-4 fusion
  - C6-7 symptomatic pseudoarthrosis
  - Tried external electrical stim unit
Note splay of spinous processes
• Return to OR 11MO PO for repair of C6-7 nonunion
  ○ C6-7 posterior arthrodesis
  ○ C6-7 instrumented lateral mass screw rod fixation
• Solid fusion by 6 months PO
Solid fusion achieved
Discussion: Comparative Studies
Fusion rates vs other graft/spacer options

- Current study: BCS + low-dose rhBMP-3, 2-4 levels
  - 98.6% fusion rate; 1 pt with symptomatic pseudoarthrosis (1.4%)

  - Retrospective, autograft or allograft, +/- plate, 1-3 levels, 1015 patients
  - 94% fusion rate for 2-level cases, 91% for 3-level cases

  - Systematic literature review, 20 studies, almost 2000 pts
  - Allograft or autograft: fusion rate = 91% levels treated
Discussion
Comparative Studies: Fusion rates vs other BCS papers

- Current study: BCS + low-dose rhBMP-3, 2-4 levels
  - 98.6% fusion rate; 1 pt with symptomatic pseudoarthrosis (1.4%)

- Lanman TH, Hopkins TJ. Early findings in a pilot study of anterior cervical interbody fusion in which recombinant human bone morphogenetic protein-2 was used with poly(L-lactide-co-D,L-lactide) bioabsorbable implants. *Neurosurg Focus* 2004;16:6.
  - BCS + rhBMP-2, 100% fusion rate (x-ray & CT), 3 mo f/u
Discussion
Comparative Studies: Complications / Dysphagia Rates

- Current study: BCS + low-dose rhBMP-3, 2-4 levels
  - 11% complication rate (7% major, 4% minor)
  - 24% prolonged & 6% persistent dysphagia rate (all resolved by 6 months)

  - 1-3 levels, 9% complication rate, 11% prolonged dysphagia rate

  - Retrospective review, 454 pts/23 sites, telephone interviews
  - Dysphagia at 3 mo: 20% 1 level, 33% 2 levels, 39% for 3+ levels
Study Strengths / Limitations

- **Strengths**
  - All consecutive patients included
  - Outcomes all prospectively collected

- **Limitations**
  - 72 pts/187 levels still small, short f/u
  - Fusion definition based on x-rays
  - Dysphagia self reported. Telephone interviews may yield a higher % of patients with persistent dysphagia
  - Did NOT use myelopathy outcome measures (MDI, JOA, Nurick, etc)
Conclusions

- Multilevel ACDF can be a very effective treatment for symptomatic cervical spondylosis, although complications rates, particularly dysphagia, can be high, as can pseudoarthrosis rates.

- Although the use of rhBMP-2 is both off-label and controversial, the results of the current study suggest that the combination of low-dose rhBMP-2 with a BCS seems to be a useful treatment option with acceptable complication rates, high fusion rates, and good clinical improvements in patients undergoing multi-level ACDF.
Thank you!