“Use of Systemic Osteoporosis Drugs in Select High Risk Patients Undergoing Spine Surgery”

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Disclosure

• Employee of Eli Lilly 2006-2016 with medical responsibility for TPTD
• Currently receive a retirement pension from Eli Lilly
• Speaker/Advisor for Radius
• Speaker for Alexion
Topics

- Spine fusion surgery intro (lumbar)
- Bone related complications of spine surgery
- Pre-operative Bone Health Assessment
- TPTD/Bisphophonate data
Spine Fusion: Definition

• Spine Fusion (arthrodesis):
  – A surgical procedure to provide internal stability of the spine, by facilitating bony interconnection between two or more of the vertebra, leading to absence of motion between these segments.

• Indications:
  – Degenerative diseases of the spine:
    • Instability, neurologic compression,
  – Deformity: scoliosis, kyphosis, spondylolisthesis
  – Trauma or tumor
Spondylolisthesis

Grades of spondylolisthesis

- Normal spine
- Grade 1: <25% slippage
- Grade 2: 25-50% slippage
- Grade 3: 50-75% slippage
- Grade 4: >75% slippage
Spine Fusion: Fusion Types

- Posterior Lumbar Fusion
- Anterior Lumbar Interbody Fusion
- Posterior Lumbar Interbody Fusion
Classic Open Posterior Lateral Fusion

(Left) In open surgery, muscles surrounding the spine are pulled back to reveal the bones. (Right) After removing portions of the bone (a decompression procedure called laminectomy), bone graft material and screws are placed along the sides of the vertebrae.
Scoliosis Correction through Posterior Approach
Spine Fusion Procedures

ALIF: Anterior lumbar interbody fusion
PLIF: Posterior lumbar interbody fusion
TLIF: Transforaminal lumbar interbody fusion
XLIF or LLIF: eXtreme lateral interbody fusion

PLF: Posteriolateral fusion

Circumferential fusion (360°): ALIF + PLF

MIS: Minimally invasive spine surgery
Minimally invasive spine surgery (MISS) is sometimes called less invasive spine surgery. In these procedures, doctors use specialized instruments to access the spine through small incisions.
Spine Fusion: Trends

Increase in spine fusion procedures in US (and other countries):

- Aging population, with desire to remain active
- Procedure improved and recovery time shortened

Highly specialized spine surgeons

- Fellowship trained (ortho and neuro) / Fusion procedure evolved: ALIF, PLF, PLIF, TLIF, XLIF, Mis-TLIF

Fusion success improved while concern remains

- Bone morphogenetic protein (BMP) experience
- ?systemic anabolic agents
- More ongoing research on osteosynthesis

Competitive innovation in device, while no systemic agents are currently approved by FDA for spine fusion

- Device companies
- FDA device division and regulation
Potential Complications of Spine Fusion Related to Poor Bone Health

- Fusion Failure (pseudoarthrosis)
- Construct/Device failure (pedicle screw loosening, interbody device subsistence)
- Proximal Junctional Kyphosis due to compression fracture of adjacent vertebral level
Spine Fusion: Fusion Failure
Failure of fusion (pseudoarthrosis) that results in significant segmental movement and eventual fracturing of the rod.
Pedicle screw loosening
Adjacent Segment Fracture (aka PJK)
## Spine Fusion Trend: US Device Market (projection)

<table>
<thead>
<tr>
<th>Type</th>
<th>2009</th>
<th>2011</th>
<th>2013</th>
<th>2015</th>
<th>Trend (‘10–’15)</th>
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</thead>
<tbody>
<tr>
<td><strong>Instrumented Thoracolumbar Fusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative</td>
<td>230,300</td>
<td>254,900</td>
<td>282,100</td>
<td>313,300</td>
<td>5.30%</td>
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<tr>
<td>Deformity</td>
<td>39,000</td>
<td>40,600</td>
<td>42,200</td>
<td>43,900</td>
<td>1.90%</td>
</tr>
<tr>
<td>Tumor/Trauma</td>
<td>33,300</td>
<td>37,400</td>
<td>41,900</td>
<td>47,200</td>
<td>5.90%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>302,600</td>
<td>333,000</td>
<td>366,300</td>
<td>404,400</td>
<td>4.90%</td>
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<tr>
<td><strong>Lumbar Spine Fusion (traditional)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior plates</td>
<td>48,690</td>
<td>50,010</td>
<td>51,290</td>
<td>52,860</td>
<td>1.40%</td>
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<tr>
<td>Posterior pedicle screw (PLF)</td>
<td>230,950</td>
<td>256,360</td>
<td>284,280</td>
<td>316,000</td>
<td>5.30%</td>
</tr>
<tr>
<td><strong>Lumbar Interbody Fusion (w/ or w/o pedicle screw)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ALIF</td>
<td>52,990</td>
<td>54,560</td>
<td>55,260</td>
<td>55,590</td>
<td>0.60%</td>
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<tr>
<td>PLIF</td>
<td>43,050</td>
<td>43,150</td>
<td>41,450</td>
<td>37,610</td>
<td>-2.80%</td>
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<tr>
<td>TLIF</td>
<td>63,480</td>
<td>85,070</td>
<td>104,390</td>
<td>126,890</td>
<td>10.70%</td>
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<tr>
<td>LLIF</td>
<td>8,730</td>
<td>17,690</td>
<td>36,280</td>
<td>60,590</td>
<td>42.80%</td>
</tr>
<tr>
<td><strong>Stand-alone IBD fusion (w/o pedicle screw)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALIF</td>
<td>18,547</td>
<td>22,370</td>
<td>24,314</td>
<td>25,016</td>
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<tr>
<td>PLIF</td>
<td>1,679</td>
<td>1,769</td>
<td>1,741</td>
<td>1,655</td>
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<tr>
<td>TLIF</td>
<td>2,158</td>
<td>3,063</td>
<td>3,862</td>
<td>4,949</td>
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<tr>
<td>LLIF</td>
<td>1,641</td>
<td>4,847</td>
<td>11,428</td>
<td>21,025</td>
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</tr>
</tbody>
</table>
Pre-operative Bone Health Assessment Prior to Elective Spine Surgery

- Maybe patients over 50? 65?
- Maybe younger in patients with glucocorticoid exposure
- Patients undergoing complicated surgery that will require decent quality bone to be successful
Severe scoliosis and rotation of thoraco-lumbar region
Morphometry Wizard Step 1 of 3

Verify the heights of T11.

If you want to redo the auto-edge finding, double-click in the exact center of the vertebra.

<table>
<thead>
<tr>
<th>M/P Ratio (%)</th>
<th>M/P Ratio</th>
<th>A/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>-1.0</td>
<td></td>
</tr>
</tbody>
</table>

Form 12/3/1926
59.0 in. 132.0 lbs. White Female
“Enhanced Prediction of Fracture Risk Combining Vertebral Fracture Status and BMD”
Siris, Genant, Laster, Chen, Misurski and Krege
Osteoporosis International  Jan 2007
Relationship Between Vertebral Fracture Grade and Bone Biopsy Results

Data were adjusted for age, height, lumbar spine BMD.


Spine fracture status is related to bone biopsy results.

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TBS a new parameter: Principles

Silva et al. JBMR 2014; Epub.
Quantitative CT: qCT

Any commercial CT scanner with appropriate software
Reference phantom
Able to isolate trabecular from cortical bone
Able to give volumetric BMD and geometrical parameters

Projectional Hip Volume Scan
Single Slice Spine Scan
Finite Element Analysis (FEA)

• Well-established method for analysis of complex structures
• Model structure as collection of “finite elements”
• Assign material properties to each element and external forces to whole model
• Compute strength or other structural performance

Crawford, Bone 2003
QCT Images (1 mm resolution)

Elastic Modulus

\( S_{\text{YLD}} = 61.4 \text{QCT}^{1.56} \)

\( r^2 = 0.78; n=53 \)

Compressive Yield Stress (MPa)
QCT Density (g/cm\(^3\))

Quantitative CT-based finite element models of the L3 vertebra from a representative study subject before and after treatment with teriparatide.

Vertebral outcomes for month-eighteen completers (full-set analysis).

PTH on Implant Fixation in Rats

- Stainless-steel screw were inserted in proximal tibia of 28 rats
- 14 rats, PTH(1-34) 60 ug/kg/day injection for 4 weeks
- 14 rats, vehicle daily injection for 4 weeks
- Histological examination showed that both groups had areas of soft tissue at the implant-bone interface, but these appeared less in the PTH group.

**PTH may enhance the early fixation of orthopaedic implants**

*Skripitz JBJS Br 2001;83:437*
Forty-five women with osteoporosis diagnosed with degenerative spondylolisthesis from one of the three treatment groups were evaluated based on: short-duration treatment (average, 5.5 months; n=15; daily subcutaneous injection of 20 µg teriparatide), long-duration treatment (average, 13.0 months; n=15; daily subcutaneous injection of 20 µg teriparatide), and bisphosphonate treatment (average, 13.0 months; n=15; weekly oral administration of 17.5 mg risedronate).

All patients underwent PLF with a local bone graft. Fusion rate and duration of bone union were evaluated 1.5 years after surgery.

Bone union rate and average duration for bone union were 92% in the long-duration treatment group, 80% in the short-duration treatment group, and 70% in the bisphosphonate treatment group, respectively.
Comparison of Teriparatide and Bisphosphonate Treatment to Reduce Pedicle Screw Loosening After Lumbar Spinal Fusion Surgery in Postmenopausal Women With Osteoporosis From a Bone Quality Perspective

Seiji Ohtori, MD, PhD, Gen Inoue, MD, PhD, Sumihisa Orita, MD, PhD, Kazuyo Yamauchi, MD, PhD, Yawara Eguchi, MD, PhD, Nobuyasu Ochiai, MD, PhD, Shunji Kishida, MD, PhD, Kazuki Kuniyoshi, MD, PhD, Yasuchika Aoki, MD, PhD, Junichi Nakamura, MD, PhD, Tetsuhiro Ishikawa, MD, PhD, Masayuki Miyagi, MD, PhD, Hiroto Kamoda, MD, PhD, Miyako Suzuki, MD, PhD, Gou Kubota, MD, Yoshihiro Sakuma, MD, Yasuhiro Oikawa, MD, Kazuhide Inage, MD, Takeshi Sainoh, MD, Masashi Takaso, MD, PhD, Tomoaki Toyone, MD, PhD, and Kazuhisa Takahashi, MD, PhD

- 62 postmenopausal women undergoing decompression and 1-2 level fusion were given either risedronate 2.5 mg/d, TPTD 20 mcg/d or no medication for osteoporosis. **OP medications were given 2 months prior to surgery and 10 months post-operatively**
- The incidence of pedicle screw loosening in the teriparatide (X-ray-CT) (7-13%) group was significantly lower than that in the risedronate (13-26%) or the control group (15-25%)
  - (P < .05)
- **Conclusion**: Our findings suggest that teriparatide increased the quality of the lumbar spine pedicle bone and reduced the loosening of pedicle screws compared with risedronate or control.
Fusion surgery for the thoracic and/or lumbar spine was performed in 29 postmenopausal women with osteoporosis.

Patients were treated with teriparatide (n = 13) or not (n = 16) before the surgery.

Patients received preoperative teriparatide therapy as either a daily (20 μg/day, n = 7) or a weekly (56.5 μg/week, n = 6) injection for a mean of 61.4 days and a minimum of 31 days.

The mean insertional torque value in the teriparatide group was $1.28 \pm 0.42$ Nm (Newton meters), which was significantly higher than in the control group $1.08 \pm 0.52$ Nm, ($p < 0.01$).

There was no significant difference between the daily and the weekly teriparatide groups with respect to mean insertional torque value ($1.34 \pm 0.50$ Nm and $1.18 \pm 0.43$ Nm, respectively, $p = 0.07$).

**Conclusion:** Teriparatide injections beginning at least 1 month prior to surgery were effective in increasing the insertional torque of pedicle screws during surgery in patients with postmenopausal osteoporosis.
Forty-three patients who started TPTD therapy immediately after surgery and 33 patients who did not receive TPTD were enrolled in this prospective case series. These patients were female, over 50, surgically treated for ASD, and followed for at least 2 years. Preoperative and postoperative standing whole spine X-rays and dual-energy X-ray absorptiometry scans, and multidetector CT images obtained before and 6 months after surgery were used to analyze the bone strength in the vertebra above the upper-instrumented vertebra (UIV+1).

After 6 months of treatment, mean hip-bone mineral density (BMD) increased from 0.721 to 0.771 g/cm² in the TP group and decreased from 0.759 to 0.729 g/cm² in the control group. The bone volume/tissue volume ratio increased from 46 to 54% in the TP group, and the trabecular bone thickness and number increased by 14 and 5%, respectively.

At the 2-year follow-up, the PJK type 2 incidence was significantly lower in the TPTD group (4.6%) than in the control group (15.2%, p=.02).

Conclusions: Prophylactic TPTD treatment improved the volumetric BMD and fine bone structure at UIV+1 and reduced the PJK-type 2 incidence.
Patients with degenerative spondylolisthesis scheduled for non-instrumented posterolateral fusion were randomized to receive 90-day subcutaneous injections with 20µg teriparatide (N = 41) or placebo (N = 46) in a 1:1 fashion. Fusion volume and quality was evaluated using 12 month postoperative fine cut CT scans.

RESULTS:

The two groups were comparable in terms of age, gender and numbers of levels operated. PTH treatment was well tolerated but provided no additional benefit versus placebo. Fusion rates, the mean volume and robustness of the fusion mass were similar between the PTH and placebo groups.

CONCLUSIONS:

90-day subcutaneous administration of 20µg teriparatide did not increase fusion volume or improve the quality of the fusion mass in elderly patients compared to placebo after non-instrumented spinal fusion surgery for degenerative spondylolisthesis.
Does alendronate disturb the healing process of posterior lumbar interbody fusion? A prospective randomized trial

Clinical article

KEN NAGAHAMA, M.D.,1 MASAHIRO KANAYAMA, M.D.,1 DAISUKE TOGAWA, M.D.,1 TOMOYUKI HASHIMOTO, M.D.,1 AND AKIO MINAMI, M.D.2

1Spine Center, Hakodate Central General Hospital, Hakodate; and 2Department of Orthopaedic Surgery, Hokkaido University, Sapporo, Hokkaido, Japan

• 40 patients randomized to ALN 35 mg/wk vs Vit D
• Single level PLIF with cage device
• CT bridging across levels graded A, B and C
• Followed for one year
• Also looked at vertebral fractures and cage subsistence
Results Continued:

- There was no pedicle screw loosening reported in either arm
- There were fewer adjacent fractures in the ALN arm zero vs 4 in Vit D arm
- Cage subsistence was seen in one ALN patient and 5 Vit D patients
- No significant difference in the Oswestry scores between groups. 3 in ALN group did poorly and 4 in D group did poorly (less than 20% improvement)...in those that did poorly pseudoarthrosis and vertebral compression fractures were common

Conclusion: Treatment with ALN in patients with OP undergoing spine fusion reduces subsequent vertebral compression fractures and cage subsistence. The mechanical circumstances of ALN treatment postop may overcome any potential detrimental biological effect on bone healing.
Seventy-nine patients were randomized to zolendronic acid (5 mg) or saline. Infusions were done 3 days after surgery.

65 women and 14 men were randomized and 69 patients completed the 12 month follow-up. All patients had single level degenerative spondylolisthesis and had OP by DXA BMD of -2.5 SD or lower at hip or spine. Patients underwent decompression and the disc material was removed. Local bone and allograft was packed space into the disc. Pedicle screws and rods were placed from a posterior approach.

Radiographic bone bridging was graded A (complete), B (bridging with one body) or C (incomplete bone bridging)
Results Continued:

• BMD was preserved in the zol arm and there was generally loss of BMD (hip) in the saline arm
• There were no adjacent vertebral fractures in the zol arm and 6 patients (17%) had fractures in the saline arm
• There was no pedicle screw loosening in either arm
• Oswestry scores were significantly better in zol compared to saline at 9 and 12 months post-surgery

Conclusion: Treatment with zol in osteoporosis patients with spinal fusion shortens the time to radiographic fusion, prevents subsequent vertebral compression fractures and improves clinical outcomes.
Conclusions

1. Older patients undergoing elective spine surgery have considerable risk for bone related complications.

2. We can assess who is at highest risk for these complications....much like we do for standard OP fracture risk assessment with emphasis on vertebral fractures.

3. Anabolic drugs appear to reduce complications and possibly improve fusion success. Anti-resorptive agents do not appear to reduce fusion success and may reduce complications like screw failure and adjacent segment fracture.
“Bare Bones”  
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Q & A

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