Biological enhancement of Aseptic Femoral Non-unions with BMP-7 – a multicenter experience.

N.K. Kanakaris, G.M. Calori, N.G. Lasanianos, R. Verdonk, P. Cherubino, T.J. Blokhuis, P. De Biase, P.V. Giannoudis

Universities of Leeds, Milan, Ghent, Nijmegen, Varese, Florence
Impaired Fracture Healing

OSTEOCONDUCTIVE SCAFFOLDS

OSTEOGENIC CELLS

GROWTH FACTORS

MECHANICAL ENVIRONEMENT

VASCULARITY

Fracture healing: the diamond concept.

Giannoudis PV, Einhorn TA, Marsh D.
Academic Department of Trauma & Orthopaedics, Leeds Teaching Hospitals, University of Leeds, UK. pgiannoud@solcom

Fracture healing is a complex physiological process. With the latest advances made in molecular biology and genetics it is now known that it involves the spatial and temporal coordinated action of several different cell types, proteins and the expression of hundreds of genes working towards restoring its structural integrity without scar formation. The standard tissue engineering approach to provide solutions for impaired fracture healing, bone restoration and regeneration includes the utilisation of growth factors, scaffolds and mesenchymal stem cells (triangular concept). However, although the mechanical environment is discussed and is considered as an important element in bone regeneration, its importance is often underestimated and it is not always given the necessary attention. The available scientific evidence supports the view that all the 4 known factors contributing to bone restoration should be given an equal acknowledgment and recognition. The traditional discussed triangular concept therefore should be reconsidered and be accepted as the diamond concept.
Femoral Non-Unions

- Are rare
- Very challenging
- Treatment may be long lasting
- Utilisation of many resources
## Reports of Femoral Fracture Treatments - Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No of patients</th>
<th>Intervention</th>
<th>Nonunion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruedi and Luscher</td>
<td>1979</td>
<td>131</td>
<td>Plating</td>
<td>7</td>
</tr>
<tr>
<td>Loomer et al.</td>
<td>1980</td>
<td>46</td>
<td>Plating</td>
<td>2</td>
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<tr>
<td>Alonso et al.</td>
<td>1989</td>
<td>24</td>
<td>External fixation</td>
<td>12</td>
</tr>
<tr>
<td>Wiss et al.</td>
<td>1990</td>
<td>112</td>
<td>Reamed antegrade nail</td>
<td>2</td>
</tr>
<tr>
<td>Riemer et al.</td>
<td>1992</td>
<td>141</td>
<td>Plating</td>
<td>7</td>
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<tr>
<td>Geissler et al.</td>
<td>1995</td>
<td>71</td>
<td>Plating</td>
<td>7</td>
</tr>
<tr>
<td>Mohr et al.</td>
<td>1995</td>
<td>17</td>
<td>External fixation</td>
<td>0</td>
</tr>
<tr>
<td>Wolinsky et al.</td>
<td>1999</td>
<td>551</td>
<td>Reamed antegrade nail</td>
<td>6</td>
</tr>
<tr>
<td>Nowotarski et al.</td>
<td>2000</td>
<td>54</td>
<td>External fixation then nailing</td>
<td>3</td>
</tr>
<tr>
<td>Ostrum et al.</td>
<td>2000</td>
<td>54</td>
<td>Retrograde nail</td>
<td>2</td>
</tr>
<tr>
<td>Tornetta &amp; Tiburtzi</td>
<td>2000</td>
<td>83</td>
<td>Reamed antegrade nail</td>
<td>0</td>
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<tr>
<td>Tornetta &amp; Tiburzi</td>
<td>2000</td>
<td>89</td>
<td>Unreamed antegrade nail</td>
<td>0</td>
</tr>
<tr>
<td>Ricci et al.</td>
<td>2001</td>
<td>134</td>
<td>Retrograde nail</td>
<td>6</td>
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<tr>
<td>Canadian Orthopaedic Trauma Society</td>
<td>2003</td>
<td>121</td>
<td>Reamed antegrade nail</td>
<td>2</td>
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<tr>
<td>Canadian Orthopaedic Trauma Society</td>
<td>2003</td>
<td>107</td>
<td>Unreamed antegrade nail</td>
<td>8</td>
</tr>
</tbody>
</table>
• Non-union was declared as healed in the absence of pain on loading and in the presence of bridging callus on 3 of the 4 cortices in two different planes on x-rays.

• One unit of BMP-7 per non-union was applied in all cases (Osigraft, by Stryker Biotech Hopkinton, Massachusetts, MA, USA) containing 3.5 milligrams of the rhBMP-7 mixed with 1 gram of type I bovine-derived collagen.

• The clinical and functional outcome assessed utilising parameters like union, complication, return-to-previous-occupation rates, and the EuroQol 5D
Patients and Methods

- A focused electronic databank has been created and updated constantly since January 2005

- Accumulation of clinical prospective and retrospective data regarding the use of BMPs

- 6 International specialised orthopaedic centres (3 Italian, 1 Belgian, 1 Dutch, 1 from UK - University hospitals)
Welcome to the BMP user group home page...

This website is intended as a data entry system and information source for decisions using Bone Marrow Proteins in their clinical practices.

It is NOT a source of patient information.

This website was designed and is maintained by the Academic Orthopaedic Trauma Department of the University of Leeds.

Current users should login for further access or to enter data.

Potential new users can apply for access via the registration page.

Further information is available within the website or by contacting a member of the administration via the contacts page.

http://www.bmpusergroup.co.uk
Results

• 30 cases (22 males - 8 females)
• Median Age 42 (range 20-78)
• 9 Smokers - 1 DM
• Mechanism: 24 RTAS – 6 Falls
• Anatomic location:
  4 proximal 1/3
  17 mid-shaft
  9 distal 1/3
Results

• 22 closed – 8 open (3 I, 1 II & 4 III)

• Initial stabilisation 15 IMN - 10 ORIFs - 5 DCO

• Previous operations 1.6 (1-5)

• Time from injury to BMP-7 application 24 months

• 10 cases had implanted AICBG

(Autogenous Iliac Crest Bone Graft)
RESULTS

- 7 cases: BMP-7 implantation - no hardware removal
- 23 cases had revision of fixation & BMP-7
  - 14 exchange IMN (11 exchange nailings and 3 revisions from ORIF)
  - 6 ORIFs (1 from IMN, 5 ORIF exchange)
  - 3 Circular Frame (1 from IMN and 2 exchanges)
- 12 cases BMP-7 and AICBG
- Median follow up 30 months (12-46)
RESULTS

• Union rate 26/30 (86.7%)
• Time to union 6 months (4-10)
• 4 cases of re-operation
• 19 patients returned to work
• 7 changed occupation
• 1 retired

• EuroQ overall health state 82.5 points
RESULTS

Complications

- 2 superficial wound infections
- 1 haematoma
- 1 DVT
- 0 systemic reactions
<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>LOE</th>
<th>Femoral nonunions &amp; BMPs*</th>
<th>Site Indication &amp; glymphMM.Hon5Union</th>
<th>Union Rates (Femur)</th>
<th>Mean time to Union (3-14)</th>
<th>Re-Operations</th>
<th>Functional Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson EE</td>
<td>1992-CORR</td>
<td>IV</td>
<td>(hBMP &amp; allograft)</td>
<td>Tibial, Femoral, Humeral</td>
<td>75%</td>
<td>6 months</td>
<td>20%</td>
<td>14 excellent 5 good 5 fair</td>
</tr>
<tr>
<td>Dimitriou R</td>
<td>2005 - Injury</td>
<td>IV</td>
<td>(BMP-7)</td>
<td>Tibial, Femoral, Humeral, Forearm, Clavicle</td>
<td>100%</td>
<td>5.6 months</td>
<td>12%</td>
<td>n/a</td>
</tr>
<tr>
<td>Calori GM</td>
<td>2008 - Injury</td>
<td>II-III</td>
<td>(BMP-7 vs. PRP)</td>
<td>Tibial, Femoral, Humeral, Forearm</td>
<td>100%</td>
<td>8 months</td>
<td>6.2%</td>
<td>n/a</td>
</tr>
<tr>
<td>Ronga M</td>
<td>2006 - Injury</td>
<td>IV</td>
<td>(BMP-7)</td>
<td>Tibial, Femoral, Humeral, Forearm, Clavicle</td>
<td>78.3%</td>
<td>7.9 months</td>
<td>16.2%</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Present Study</strong></td>
<td></td>
<td>IV</td>
<td>(BMP-7)</td>
<td>Femoral</td>
<td><strong>86.7%</strong></td>
<td><strong>6 months (4-10)</strong></td>
<td><strong>13.3%</strong></td>
<td>21 excellent 5 good 4 poor (re-operation)</td>
</tr>
</tbody>
</table>
Case 1

(female - 73 years old - RTA)

A. Left Spiral shaft femoral fracture treated with locking LISS MIPPO plating
B. Nine months later no progress of healing.
C. Intramedullary nail fixation and BMP7 application (9 months post injury).
D. Five months later, pain free function of the extremity and radiological healing.
Case 2

(male - 24 years old - RTA)

A-B. Femoral supracondylar fracture 12 months post injury and after an original ORIF and a first revision ORIF with locking LISS plate.

C. Postoperative films after revision ORIF with a blade plate and BMP-7 application.

D. 8 months post BMP7 application evident radiological healing, pain free FWB.
Case 2
Case 3

(male - 62 years old - fall )

A. Subtrochanteric right femoral fracture.
B. Initial IMN fixation. Malreduction in varus angulation and distraction.
C. 18 months post initial fixation and after a failed exchange nailing.
D. Revision of the nail and application of BMP7 and Autograft.
E. 6 months post BMP7 application, evident radiological and clinical healing.
- No statistical differences between cases treated with BMP-7 or Autologous Bone Graft in tibia non-unions
  
  **Literature**
  
  Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions.

- Osteomyelitis at the fracture site in 21 % of patients treated with ABG but only in 3 % of those treated with BMP-7
  
  **Literature**
  
  Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions.

- BMP-7 reduces consolidation time in the scaphoid non-union compared to the time needed after the use of ABG.
  
  **Literature**
  
  Osteogenic protein-1 (BMP-7) accelerates healing of scaphoid non-union with proximal pole sclerosis.

- Clinical and radiological union at a percentage of 92.3 % in persistent upper and lower limb non-unions
  
  **Literature**
  
  Application of recombinant BMP-7 on persistent upper and lower limb non-unions.

- The implantation of BMP-7 in pelvic reconstruction procedures adds another alternative to the treatment methods of contemporary orthopaedic
  
  **Literature**
  
  Biological enhancement of bone healing with Bone Morphogenetic Protein-7 at the clinical setting of pelvic girdle non-unions.
  Giannoudis PV, Psarakis S, Kanakaris NK, Pape HC. - *Injury* 2007; 38 Suppl 4 S43-8

- Treating fracture non-unions is costly, but this could be reduced by early BMP-7 administration when a complex or persistent fracture non-union is present or anticipated.
  
  **Literature**
  
  Biological enhancement of bone healing with Bone Morphogenetic Protein-7 at the clinical setting of pelvic girdle non-unions.
  Giannoudis PV, Psarakis S, Kanakaris NK, Pape HC. - *Injury* 2007; 38 Suppl 4 S43-8
Conclusions

- The implantation of BMP-7 as a biological stimulant appears to offer a good alternative option to AICBG.

- Use them in an early stage to avoid many re-operations

- No donor site morbidity – ABG harvesting

- Union rates as good as other series - No systemic effects.

- Need for multicenter supported databanks
Application of BMP-7 to femoral non-unions: A 4-year multicentre experience

N.K. Kanakaris*, N. Lasanianos, G.M. Calori, R. Verdonk, T.J. Blokhuys, P. Cherubino, P. de Biase, P.V. Giannoudis*

*Department of Trauma and Orthopaedics, Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Leeds, UK
+Department of Trauma and Orthopaedic Surgery, University of Milan-Bicocca, Milan, Italy
#Department of Orthopaedics, Ghent University Hospital, Ghent, Belgium
*Department of Surgery and Transplantation, University Nijmegen Medical Centre, Nijmegen, Netherlands
%Department of Orthopaedics and Trauma Sciences, University of Milan, Milan, Italy
&Department of Trauma and Orthopaedic Surgery, Azienda Ospedaliero Universitaria Senigallia, Senigallia, Italy

THANK YOU

Universities of
Leeds, Milan, Ghent, Nijmegen, Varese, Florence