The Bone & Joint Journal

Journal club: 16 January 2013
Chairmen: Mr A Ajuied & Miss D Back
Convener: Mr A Vasireddy
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Theme: The use of Bone Graft in Trauma Surgery

Pape HC, Evans A, Kobbe P. Autologous bone grafts: properties and techniques. *J Orthop Trauma* 2010;24 (suppl 3).

Reviewer: Mr Sarvpreet Singh, ST6

Background
Review article on the topic of autolougous bone grafting.

Aim
To summarise the biological and mechanical properties of autologous bone grafts; differentiate various autologous bone graft types; and, compare them with other bone substitutes.

Methods
Review article of about 58 references.

Results
Autologous bone grafts remain the gold standard due to their superior osteogenic, osteoinductive and mechanical properties.

Conclusion
Autologous bone grafting is an excellent and cost-effective option. It is an important tool in the management of Nonunion and bone defects because it possesses both biological and mechanical properties.

If heterologous or synthetic bone is combined with growth factors, these composite grafts may have similar biological properties to autologous bone grafts but further research is required to determine their effectiveness and cost benefit profile.

In clinical practice, when deciding on the specific bone graft type to use, one must consider whether the operative site needs metabolic activity (cancellous), stability (cortical bone), or both.

Recommendation for our practice

The decision to use bone grafts should be determined by the specific pathology that one is attempting to correct, i.e. is it biology or the mechanics or both.

Giannoudis PV, Kanakaris NK, Dimitriou R, Gill I, Kolimarala V, Montgomery RJ. The synergistic effect of autograft and BMP-7 in the treatment of atrophic nonunions. *Clin Orthop Rel Res* 2009;467:3239-3248.

Reviewer: Christian Smith

Background
Nonunion occurs in up to 10% of fractures. Nonunions can be divided into hypertrophic or atrophic and septic or aseptic. Atrophic nonunions are notoriously difficult to treat and often require multiple operations and are associated with a very long recovery. The treatment of atrophic nonunions is based on the enhancement of the biology of the native bone. The gold standard is currently the use of autologous bone grafting (ABG) into the fracture site. One of the most recent techniques involves the use of bone morphogenic protein 7 (BMP-7) which has been shown to be osteoinductive and angiogenic. Many studies have looked at the use of BMP-7 as an alternative to ABG.

Aims
The paper aimed to assess the synergistic effect of using ABG in conjunction with BMP-7, whether it is superior to ABG or BMP-7 treatment alone. The group used a combination of ABG and BMP-7 to treat atrophic nonunions, monitoring the healing rate and time, limb function and complications from the intervention.

Methods
The paper is a case series and as such is only level 4 evidence. It was ethically approved. Patients were recruited into the study over a 4 year period from October 2003 until December 2006. 45 patients were included, all of which had previously endured a previous unsuccessful operative intervention for atrophic Nonunion of a fracture. 35 patients had fixation revision at the time of ABG and BMP-7 application. All fractures had tissue samples taken to exclude infection. 3.5g of recombinant human BMP-7 was mixed with 1g type 1 bovine derived collagen (Stryker Biotech, Hopkinton, MA). This substance was then used with autologous iliac crest bone graft. Early passive and active mobilisation was encouraged and clinical and radiological signs of healing governed weight-bearing status. The endpoint of the treatment was governed by time to pain free limb function, return to work and radiological union.

Results
The median duration of atrophic Nonunion was 20 months prior to ABG and BMP-7 combined use. 32 males and 13 females were included, with a median age of 43 (range 19-76). There were 7 humeral, 19 femoral and 19 tibial fracture nonunions.
100% of fractures progressed to clinical healing, with a median time of 5 months. Radiological healing was achieved with a median time of 6 months. The skin healed in 100% of patients. There was no reports of deep infection, DVT or neurological deficit or any adverse reactions to BMP-7 use. A visual analogue scale for pain at the time of the final follow up had a median score of 0.9 (range 0-2.8). A functional scoring questionnaire scored a median value of 86/100 (range 67-95).

87% of patients returned to work. Of the patients that did not return to work, they all had a pain VAS score greater than 2 and a functional questionnaire score of less than 70.

Discussion/Conclusions
Treating atrophic nonunions can be time consuming, expensive to the health services and is often unsuccessful. The idea of graft expansion is to biologically enhance autologous bone grafting. Although this study was only a case series, a reverse power calculation revealed 180 patients would need to be recruited in order to demonstrate a 10% increased healing effect size with 80% power. Previously documented concerns over BMP-7 use (osteolysis, heterotopic ossification and anaphylaxis) were not encountered in this study. Reports from a previous study by Friedlaender et al reported osteomyelitis in 3% of cases with BMP-7 and 21% with ABG.

Our Conclusions/Appraisal
This descriptive study is a case series of 45 patients; therefore level 4 evidence. As a result there was no control group and no form of randomisation to treatment. A reverse power calculation determined that 180 would need to be recruited if an expanded study was designed. Inclusion criteria helped remove any selection bias, all atrophic nonunions presenting in 2 hospitals over a 4 year period were enrolled. Unfortunately the fact that 3 different bones were treated (i.e. humeral, femoral and tibial atrophic nonunions) prevented comprehensive statistical analysis, as each group was too small. The group showed a good intention to treat; 100% of patients were followed up to the end point after a minimum of 12 months.

The paper achieved its aim, and included a reasonable number of patients to infer some meaningful message. Patients were well followed up and suitable end points were used for the study. It is a significant paper and provides preliminary evidence, which can be used to plan a much larger study.

Recommendations for our Practice
Consider the use of BMP-7 in synergy with ABG in the treatment of atrophic nonunions. Further evaluation is needed.

Kanakaris NK, Lasanianos N, Calori GM, Verdonk R, Blokhuis TJ, Cherubino P, De Biase P, Giannoudis PV. Application of bone morphogenetic proteins to femoral Nonunions: a 4-year multicentre experience. *Injury* 2009;40 (Suppl 3):S54-61.

Reviewer: Jerome Davidson

Background
Nonunions of femoral fractures are both rare and very challenging since their successful treatment may be prolonged and may exploit numerous resources.

Aims
The aim of this investigation is to present a comprehensive analysis of a multicentre prospective effort to systematically record and evaluate the results of BMP-7 application in the treatment of aseptic femoral Nonunions.

Methods

This study is a multicentre case series. Patients are identified by the use of a multicentre database. Level 4 evidence. Six international centres are used which record information onto the 'bmpusergroup' database. Data was collected prospectively and retrospectively. Patients were included if they had an aseptic femoral Nonunion and BMP-7 was used in the treatment of their Nonunion. An established femoral non union was one that was considered greater than 9 months. Overall follow-up should have been longer than 12 months. 1 unit of the BMP 7 (Osigraft, Stryker) was used in each case for treatment of the Nonunion. Surgeons were able to use autograft in addition to the BMP if there was a defect greater than 1cm.

Results

The series comprised 30 consecutive cases of femoral aseptic atrophic Nonunion treated with BMP-7. 8 were women and 22 were men, with an average age of 42 years. All the original injuries were femoral fractures. 20 cases were due to motor vehicle collisions; 4 cases as a result of motorcycle accidents; and, 6 as a result of falls. 17 fractures were localised to the femoral shaft, 4 affected the subtrochanteric region and 9 affected the supracondylar region.

The initial treatment method varied. 15 fractures were treated by intramedullary nailing (IMN) and 10 underwent open reduction internal fixation (ORIF) with a plate. External fixation was applied to five fractures as a damage control procedure.

The median time from initial injury to BMP-7 operation was 24 months (range 9 to 65, mean 27.5 months).

The median follow-up in these cases lasted 30 months (range 12 to 68, mean 31.2 months). The union rate for that period of time was 86.7% (26 healed Nonunions), and the median time to union was recorded as 6 months (range 4 to 10, mean 6.2 months). Four people did not progress to successful healing of their non union.

No statistics were used.

Discussion/Conclusions

The present report describes the preliminary results of the management of femoral Nonunions using BMP-7 in six different European university centres over a period of almost 5 years. The fact that this is an observational study without a control group. As such, this is a case series with it's associated limitations. However, this research does present the actual clinical reality and reflects the current clinical practice of these six university centres.

Our Conclusions/Appraisal

This study is a case series and is limited by a relatively low study number and lack of statistical analysis. The results may also be influenced by the differing strategies of fixation followed in the contributing centres, the numbers and skills of the surgeons involved and the differences between patient populations. However, it attempts to make a sensible approach to a complicated problem by describing the use of expensive new BMP substance in the treatment of aseptic Nonunions of the femur. The paper noted no adverse effects to the use of BMP in these patients. However, this is too small a sample to make the assumption that it is therefore safe.

Pieske O, Wittmann A, Zaspel J, Löffler T, Rubenbauer B, Trentzsch H, Piltz S. Autologous bone graft versus demineralized bone matrix in internal fixation of ununited long bones. *J Trauma Management & Outcomes* 2009;3:11.

Reviewer: Fabian Wong

Background
Nonunion of fractures, an uncommon but significant complication in orthopaedic surgery, is treated with open reduction and internal fixation (ORIF) and augmented with bone grafts. The gold standard treatment is autologous-bone-grafting, although allografts have since been introduced into the current market and could readily be used off the shelf.

Aims
The aim of this study, therefore, is to evaluate and compare the "healing characteristics of ununited bones treated with ORIF combined with either iliac-crest-autologous-bone-grafting (ICABG) or demineralised-bone-matrix (DBM)".

Methods
This is a retrospective cohort study of consecutive patients who presented to a single Level I trauma centre over a 7 year period, with nonunion of upper and lower limb long bone fractures. Nonunion was defined as "the lack of bone healing by at least six months after fracture". Treatment involved ORIF with ICABG or DBM augmentation.

Other inclusion criteria were:
adult patients
atrophic and diaphyseal nonunion
absence of a segmental defect
closed fracture or Gustilo grade 1 fracture
absence of infection

All the patients included in the study were followed-up for 12 months following the index procedure. In addition, they did not have more than one procedure.
Patients were excluded if they had pathological fractures due to malignancy or had a history of severe systemic disease, immunosuppressive therapy, or reflex sympathetic dystrophy.
Patients who were given a bone-grafting material other than ICABG or DBM, were also excluded.
This is a study of Level IV evidence.
Statistical analysis was performed using Mann-Whitney U test for non-parametric data and Spearman Correlation Coefficient for various demographic factors.

Results
There was no difference in patient demographics between the treatment groups, with the exception of a higher ASA category in patients who were given allograft.
The mean follow-up was 56.6 months (18-87 months) and 41.2 months (12-69 months) in the ICABG and DBM groups, respectively.
There was no difference between the mean time period to clinical healing or the time period to radiological consolidation. In the ICABG group, 2 of the 10 patients had failed to demonstrate bone bridging and represented cases involving forearm fractures. However, there was no statistically significant difference in healing rate between groups.

2 patients from the ICABG group also developed donor site complications, with a lower overall patient satisfaction.
There was no correlation between Nonunion consolidation and patients' smoking behaviour, age, sex, BMI and ASA status.

Discussion/Conclusions
Autologous bone graft is the current gold standard in augmented ORIF for long bone Nonunion in upper and lower extremities. DBM is equally effective in comparison to autologous bone graft in these situations. There is no associated donor site morbidity with DBM and, as a result, it appears to have a higher patient satisfaction.

Our Conclusions/Appraisal
This study reported all long bone Nonunions in upper and lower extremities, treated with ICABG or DBM. Both are commonly available graft materials that are relevant to daily orthopaedic practice. The authors have defined what they considered as Nonunion, proposed a valid methodology including a minimum follow-up period, and utilised valid statistics. Their conclusions were drawn from their results and complications were also reported.
However, this study has a very small sample size and predisposes to a type II error. In addition, the smoking status of the patients was described in mean pack years, which is likely to contribute to analytical bias and skew the results. Only 3 of the 20 patients were smokers. While the effect of smoking on fracture healing is well documented in the current literature, a more appropriate method would be to simply correlate failure to union and whether the patient was a non-smoker.
Finally, although no isolated correlation was found between union and the location of Nonunion or type of fixation used, there could be a correlation when these factors were combined in a multivariate analysis.

Recommendations for our Practice
There is no evidence to suggest either DBM or ICABG is superior in stimulating the healing of fracture Nonunion. Where the need for bone graft material is anticipated pre-operatively, discussion with patients should take place in order to ascertain the preference of the patient and the surgeon. Risks and complications, including donor site morbidity from autograft harvesting, as well as potential concerns in using allograft should be explained. In addition, further studies would be required in the form of randomised controlled trials involving large sample sizes and a cost analysis study. Such studies would help provide a definitive answer to this research question.

Zimmermann G, Wagner C, Schmeckenbecher K, Wentzensen A, Moghaddam A. Treatment of tibial shaft Nonunions: bone morphogenetic proteins versus autologous bone graft. *Injury, Int. J. Care Injured* 2009;40:S50–S53

Reviewer: A Vasireddy

Background
Fracture healing is a complex physiological process. This process can fail for a number of reasons with rates of Nonunion of 10% in all fractures and up to 50% in open tibial fractures. Nonunion can be managed by a number of techniques, which include exchange nailing, dynamisation, plating and autologous bone grafting. However, many patients need more than one operation to aid healing.

Aims

To determine and compare the success rates of autologous bone grafting with and without the administration of BMP-7.

Methods

Comparative study with historical controls
Level of evidence 3
2 cohorts used.

The historical cohort is group of 82 patients who were recruited from 1995 to 2002. These patients had tibial shaft nonunion diagnosed at 4 months post fracture fixation. These patients were then treated with autologous bone graft +/- revision fixation as necessary. Nonunion after bone grafting was defined as failure of radiological union at 20 weeks post-op.
26 patients with nonunions were recruited between 2002-2005 to form the BMP-7 cohort. All patients had already been treated with autologous bone graft at least once. After surgery with BMP-7 +/- bone graft +/- revision fixation, were followed-up prospectively at regular intervals. Nonunion, if it occurred, was diagnosed at the 3 to 4-month interval.
Patients were followed up for 1 year. Plain radiographs were used for imaging purposes. On occasion, CT scans were also undertaken if required.
Both groups were tested for epidemiological homogeneity. Factors that were assessed included age, gender, AO classification, open fracture classification, NSAID use, smoking and diabetes.

Statistical tests to be used included chi2-test, Fisher's exact test and Wilcoxon testing all via SPSS.

Results

The two groups were similar in terms of age and gender bias. There was no significant difference between the two groups in terms of AO fracture type, open fracture classification, NSAID use, smoking and diabetes.
In the historical cohort group, the average time from injury to bone graft surgery was 11 months. All patients underwent revision fixation as well. 58 of the 82 patients achieved consolidation of the fracture (71%).
Patients in the BMP-7 group underwent an average of 4 previous procedures. During the BMP-7 surgery, the treatment paradigm was incredibly heterogeneous. 8 patients underwent BMP-7 implantation only. 10 patients underwent BMP-7 implantation with revision fixation. The remaining 8 patients underwent BMP-7 implantation with autologous bone grafting and revision fixation. Overall, 24 out of 26 patients achieved bony consolidation (92%). Of the two patients that did not achieve union
Statistics were valid but the groups were small and only the chi2 results are described.
No a priori or post hoc power analysis.

Discussion/Conclusions

Relatively few studies exist that be used to compare with the results of this particular study. The patient numbers are low in both groups. Although the groups are comparable in terms of epidemiological data, they are very different in terms of clinical issues. For example, the BMP-7 group had had many previous procedures prior to the most recent surgery. The control group was historical and assessed prospectively.

Overall, the bony consolidation rate was higher in the BMP-7 group compared to the autologous bone-grafting group only. This was despite the fact that the BMP-7 group had many previous procedures and 'worse histories'. Nonetheless, the case numbers are too small to make definitive conclusions as to whether BMP-7 is superior to autologous bone grafting.

Our Conclusions/Appraisal

The purpose of the study was clearly documented.

Study design:

Small cohorts were used. However, patient groups were matched for demographics. As the numbers were small, it was inappropriate to undertake any subgroup analysis and stratify patients according to injury severity or similar factors.

Treatment:

A standard follow-up protocol was used for the prospective BMP-7 group. However, the previous treatments that patients had received were variable and were not standardised. Details of the overall surgery technique are described but patients underwent a variety of different surgical options within the BMP-7 group (e.g. BMP-7 only vs. BMP-7 + revision fixation +/- autologous bone grafting).

Assessment:

Bony consolidation is the primary outcome measure of the study and was diagnosed on a radiological basis. The follow-up protocol was clearly described for the prospective BMP-7 group. Functional outcomes were not explored.

Statistics:

No a priori or post hoc stats modeling. A p value is given in the study showing a statistically significant difference between bony consolidation rates of the historical group vs. the prospective BMP-7 group. However, the low patient numbers make it difficult to make definitive conclusions about the study - a limitation that is clearly explained in the article.

However, the high bony consolidation rate in the BMP-7 group with 'worse histories' and many previous surgeries does suggest that BMP-7 does have a role to play in Nonunion surgery.

Recommendations for our Practice

Treatment of patients has to be individualised. Identify the cause of the delayed / Nonunion. Try to be proactive, e.g. encourage smokers to stop smoking at their initial presentation to hospital; optimise medical co-morbidities, etc.

Remember the Diamond concept as described by Giannoudis. The main factors that dictate fracture healing are vascularity, growth factors, mesenchymal cells, scaffold and mechanical stability. Identify the cause and treat specifically with a tailored regimen.