The Bone & Joint Journal

Journal Club: 1 October 2012
Attendees: R.M. Dominic Meek, Mr N. Wilson, Mr A.S. Brydone, Mr D.F. Russell, Miss E.J. Baird, Mr I. McGraw, Mr A.J. Wilkinson
West of Scotland Journal Club, Western Infirmary, Glasgow

Theme: Bone Biology and Statistics

1. **Petrie A.** Statistical power in testing a hypothesis. *J Bone Joint Surg [Br]* 2010; 92-B:1192-94.
2. **Park MS, Kim SJ, Chung CY, Choi IH, Lee SH, Lee KM.** Statistical consideration for bilateral cases in orthopaedic research. *J Bone Joint Surg [Am]* 2010;92-A: 1732-37.
3. **Giannoudis PV, Einhorn TA, Marsh D.** Fracture healing: the diamond concept. *Injury* 2007; 38 Suppl 4:S3-6.
4. **Delloye C, Cornu O, Druez V, Barbier O.** Bone allografts: What they can offer and what they cannot. *J Bone Joint Surg [Br]* 2007;89-B:574-9.

Petrie A. Statistical power in testing a hypothesis. *J Bone Joint Surg [Br]* 2010; 92-B:1192-94.

Reviewer: Mr F. Mahmood

Summary

1. Purpose
To review of techniques used to determine adequate study population sizes using power calculations.

2. Review
This annotation explores the utility of power calculations in determining appropriate study population sizes for comparing methods of treatment. The author uses an example of a study comparing blood loss in two populations of patients with intertrochanteric hip fractures; one treated with a compression hip screw, the other with a percutaneous compression plate. He uses this example to define statistical terminology such as the null hypothesis, p-values and power. Factors affecting power – the significance level, variability in the data and sample size are reviewed. The importance of an adequately powered study is demonstrated, whilst potential issues with overpowered studies are also highlighted.

The paper then demonstrates how a power calculation might be performed. Different methods such as statistical tables, equations, computer programs and diagrams are mentioned. A worked example using the study mentioned above is provided using a power calculation technique known as Lehr's formula.

The author then explains the technique for a retrospective power calculation to determine whether a study has in fact been performed adequately. Finally, the paper provides a lengthy glossary of statistical terminology related to power calculations.

3. Study critique

Strengths
The paper provides a comprehensive review of the methodology related to power calculations, importantly, it does not restrict itself to explaining power calculations alone, but also gives an overview of the statistical terminology related to clinical research. The glossary is helpful in deciphering some of the more dense material in the paper.

Weaknesses
The section on conducting the power calculation itself is rather limited, a number of different methods are referred to but little detail is provided. It may have been more useful to refer to other sources of information or include some more worked examples using diagrams and statistical tables.

Park MS, Kim SJ, Chung CY, Choi IH, Lee SH, Lee KM. Statistical consideration for bilateral cases in orthopaedic research*. J Bone Joint Surg [Am]* 2010;92-A: 1732-37.

Reviewer: Miss E. J. Baird

Summary

1. Purpose
To describe the application of bone allografts in a clinical setting.

2. Review
This paper was published in JBJS (Br) as part of the 'Aspects of Current Management' review series, from Professor Delloye in Brussels. The introduction covers the increasing use of bone allografts, and the unique properties of bone as a graft substance. Any allografts should be held up in comparison to the gold standard: cancellous autograft.

The paper summarises the characteristics of bone graft and the host bed, providing clear definitions of osteogenic, osteoconductive and osteoinductive properties. The goal of grafting is to initiate a healing response, form new bone at the host-graft interface and within the porous body of the graft material. Key concepts to achieve this are mechanical stability and vascularity of the host bed. Transmission of disease is covered briefly, in terms of the potential organisms, and the screening of donors, tissue quarantine and processing. The sources of bone are detailed: living donors (such as femoral heads retrieved at total hip replacement), multi-organ donors (procured for national tissue banks), and bone obtained post mortem. Processing of the bone involves harvesting in aseptic conditions (or irradiated at the final stage), shaping and sizing, inactivation and removal of harmful agents, marrow and debris, and treatment with ethanol, acetone, ether or hydrogen peroxide. Bone is prepared by freezing at 0^{o}C, freeze drying, or with liquid nitrogen. The paper details types of bone allografts, and the advantages and disadvantages of each: cortico-cancellous (e.g. unprocessed frozen femoral heads), osteoinductive (e.g. demineralised bone matrix mixed with calcium sulphate, collagen or bioglass) and massive structural allografts, defined as more than 5 cm in length and including the full circumference of the bone. These can be osteochondral, intercalary, segemental with arthodesis or prosthesis, or as a cortical strut. Finally, the paper covers the requirements of a bone allograft; namely, good quality, safe, demineralised, strong and easy to handle. The limitations of allografts are that the mechanical and biological characteristics are not reproducible, and clearly, they cannot be lengthened once inserted! A final paragraph summarises nicely: ‘A successful result with allograft is an interaction between three parties. The surgeon has to define his need, prepare the host bed and handle and fix the graft. The tissue bank selects and screens the donor. It then prepares and chooses the bone according to its intended use. The patient must be fit enough to allow successful healing of the graft, and must comply with the prescribed post-operative treatment.’

Critique

Strengths

Excellent summary of what has the potential to be a dry topic.

Well pitched at a level appropriate from everyday clinical practice and FRCS preparation, with very helpful definitions of key terms.

A well-referenced review of the topic, from a recognised expert in the field.

Weaknesses

Aim of the paper ‘what it can offer and what it cannot’ was not clearly answered, as it appeared as if perspective of the paper was more one of a tissue bank, than of a clinician using bone grafts.

Giannoudis PV, Einhorn TA, Marsh D. Fracture healing: the diamond concept. *Injury* 2007; 38 Suppl 4:S3-6.

Reviewer: Mr I. McGraw

Summary

1. Purpose

To describe and provide a scientific basis for a new concept of fracture healing.

2. Review

This article was published as part of the 4th European Clinical Symposium on Tissue Engineering and Bone Regeneration.

The authors begin by noting that bone tissue has reparative abilities that allow self-repair without formation of scar tissue and pre-fracture properties are mostly restored.

It is noted that previously a triangular concept has been described when considering factors required to aid bone healing. These are namely; a viable and vibrant cell population, a stimulus from signalling proteins and a scaffold of either graft or substitute

The authors argue the importance of mechanical stability is often underrated and suggest a conceptual addition of the mechanical environment. They suggest this has equal importance and argue more attention should be directed towards the mechanical stability in microenvironments regardless of whether gold standard autograft or synthetic substitute is used.

The paper then summarises both forms of fracture healing and states that the cell population is of initial importance and indeed the 'mandatory first element'. Multipotent mesenchymal cells are recruited at the injury site or via circulation and the bone marrow responds with reorganisation of cellular population, increasing cell density at the fracture site. These mesenchymal stem cells then undergo osteoblastic transformation. The authors note that genetically engineered MSC and differentiated osteoblasts have been utilised to enhance fracture healing

Second in their diamond concept is the importance of signalling molecules. Those highlighted are the interleukins (IL1 and IL6), TNFα, growth factors (FGF, IGF, PDGF) in particular the vascular endothelial growth factor (VEGF) and the TGFβ superfamily members. These signalling molecules are secreted by endothelial cells, platelets, macrophages and monocytes as part of inflammatory response and more specifically are also secreted by MSC, chondrocytes, osteocytes and osteoblasts. The authors remark that clinical use of these has increased dramatically over last 10-15 years most notably with the use BMP-2 and BMP-7 which belong to TGF β superfamily

Third in their concept is the extra-cellular matrix or scaffold. They note that study into the use of osteoconductive materials alone or enriched with osteogenic and osteoinductive factors has led to a host of products widely available on the clinical market from allograft to xenograft, demineralised bone matrix, collagen based products, hydroxyapatite and calcium based ceramics.

The 4th element they wish to introduce is the concept of mechanical stability. They state this is crucial in order to progress from mature callus to woven and lamellar bone and was really first described with Wolff's law in 1892. The complexity of this was initially appreciated with 1950's AO teaching to the more modern concept of 'biologic fixation' and the importance of concepts such as implant rigidity, relative or absolute stability, fracture gap size and interfragmentary strain. The authors state that "*relative* stability plus respect of the soft tissue envelope is now considered *essential* and it is important to minimise fracture gaps and keep strain below 10%'. The importance of this is taken further with the concept of microenvironment stability. It is stated that the stability of grafts, scaffolds or graft carriers are often overlooked and the properties of these vary greatly with respect to architecture as well as porosity. They state that the quality and density of host bone bed should differentiate which materials are used and qualify this by saying that 3D porous polymer scaffolds with pore sizes ranging from 150-500μm have shown optimal results related to biomechanical properties. It is conceded however that in context of fixation with graft/substitute the required stability for optimal healing is not known and presume that a load-shielding period to protect initial phase of graft incorporation would be important.

In summary the authors conclude that as well as the degree of fracture stabilisation (whether operative or non-operative) itself, the mechanical environment where any graft material is expected to act has *equal* significance to its own biologic properties (regardless of whether it is autograft or synthetic substitute).

Critique

The authors provide a clearly written and succinct summary of fracture healing. The paper promises a revolutionary theory regarding fracture healing but in fact nothing ground breaking is described. There is really so much more we don't know regarding this field and this is demonstrated with the evidence the authors present to support their statements. Small in vitro and animal studies, some dating from more than 10 years ago, are used to support their view. The main conclusion however that mechanical stability across the fracture and in the micro environment has equal significance is not backed with clear evidence to support this view. Nonetheless what is of value here is the opportunity for the reader to learn the understanding and views regarding this fascinating field from three authors who are world leaders in their field.