Enhancing Bone Healing

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Overview

- Bone healing
  - Primary
  - Secondary
- Enhancing bone healing
  - Physical
  - Biological
- Future
Bone Healing - Primary

- Rigid stabilisation and anatomic alignment
- Little to no callus
- Types:
  - Contact Healing
  - Gap Healing
Primary Bone Healing

- Contact Healing

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Primary Bone Healing

- **Gap Healing**: <1mm gap and <2% interfragmentary strain
Secondary Bone Healing

- Inflammatory
  - Ischaemic bone necrosis
  - Hematoma
  - Fibrin mesh

- Repair
  - Granulation tissue
  - Connective tissue
  - Soft Callus
  - Hard callus
Secondary Bone Healing

- Remodelling
  - Balanced osteoclastic resorption and osteoblastic deposition by Wolff's Law

Role of Growth Factors and Inflammatory Mediators

Picture from Bojrab & Monet 2010: Mechanisms of Disease in Small Animal Surgery
Enhancing Bone Healing

- Indications
  - Arthrodesis
  - Delayed/Non-union
  - Osteomyelitis
  - Large bone defects – trauma or neoplasia
  - Fractures with reduced healing potential
    - Host healing potential
    - Local environment
  - Spinal fusion
Enhancing Bone Healing - Physical

- Altering mechanical environment
- Mainly human studies & applications
  - Destabilisation (-)
  - Induced micromotion (?)
  - Dynamisation (-)
  - Electrical stimulation (+?)
    - Direct current stimulation
    - Pulsed electromagnetic fields
    - Capacitive coupling
    - Combined magnetic fields
  - Low-intensity Ultrasound (+?)
  - Extracorporeal shock wave therapy (+)

Picture from http://www.vegao.co.uk
Enhancing Bone Healing - Physical

- Destabilisation
  - Stable fixation -> decrease stiffness of fixation as fracture heals and develop strength
- External fixators
- Early studies suggest increase callus formation
- Auger et al 2002 (Vet Surg)
  - 12 dogs (type II ESF control vs destabilisation – single & multistaged)
  - No significant advantage with destabilisation
  - Not technically enhancing bone healing, but preventing stress protection.
Enhancing Bone Healing - Biological

Strategies/ Properties of materials

- **Osteoinduction**: Recruitment of mesenchymal cells or their progeny (chemoattraction or migration) Induction multipotential cells to multiply and contribute to bony callus production.

- **Osteoconduction**: 3D scaffold to provide framework to allow ingrowth of cells, vessels and tissues.

- **Osteogenesis**: Supply and support osteogenic cells (mesenchymal stem cells and osteoblasts). Early cellular environment is important.

- **Mechanical/Structural support**: Load bearing characteristics during bone regeneration.

- **Osteopromotion**: Enhances bone regeneration via introduction of substances or materials, or by physical and mechanical strategies that induce proliferation and differentiation of mesenchymal stem cells and their progeny. E.g. platelet rich plasma.
Autogenous cancellous graft

- Fulfils almost all strategies/properties except mechanical support
- Major setback is limited supply
  - Hence substitutes required
- Complications – rare
  - Fracture, premature physeal closure
  - Morbidity mostly from human studies (iliac crest)
- Increased time & anaesthetic – low consequence
Alternative approaches

- **Matrix based**
  - Synthetic biomaterials
  - Demineralised bone matrix
- **Factor based**
  - Growth factors & Bone Morphogenetic Proteins (BMPs)
  - Gene therapy
- **Cell based**
  - Bone marrow
  - Mesenchymal stem cells (MSC)
Matrix based

- Synthetic biomaterials – extensive!
  - Calcium phosphates
  - Ceramics
  - Bioglass
  - Coral-derived products
  - Polymers (Polylactic/polyglycolic acid)
  - Etc etc etc

- Pore size and porosity is important. Ideal pore size of 300-500 microns as minimum 100 microns required for osteoid formation
Demineralised Bone Matrix (DBM)

- Allograft and species specific
- Prepared from ground bone and decalcification with acids leaving non collagenous proteins, growth factors and collagen.
- Direct osteoinduction without resorption
- Available in multiple forms (putty, gel, paste, mix, strips)
- Review article in VCOT 2010;23:393-399 (Innes et al)
- Basic science, experimental animal work and human clinical experience supports the use of DBM as an bone graft substitute.
Demineralised Bone Matrix

- Hoffer et al 2008 (Vet Surg, 37;639-647)
  - Retrospective case matched* study of 75 dogs with clinical application of DBM.
  - Cases include fracture repairs (33), * arthrodesis (16), *TPLO (15) and corrective osteotomy (7)
  - Surgeon assessment allowed TPLO dogs with DBM to return back to normal function 2 weeks earlier
  - Arthrodesis cases had similar outcomes
  - Complication rates comparable 19%
- Future randomised trials warranted
Factor Based

- BMPs *
- Growth factors
  - Fibroblast growth factor
  - Insulin-Like growth factor
  - Platelet-Derived growth factor
- Platelet rich plasma *
- Gene therapy
BMPs

- Subfamily of the TGF–β family
- Stimulates pluripotent mesenchymal cells to differentiate into osteoblasts.
- Extensively studied especially BMP-2 and 7 (OP-1)
- Recombinant gene technology used to make recombinant human BMP (rhBMP)
- Interspecies homology is 100%

BMPs

- Numerous studies demonstrated efficacy in enhancing bone repair both in humans and animals
- FDA approval for rhBMP2 and 7 in use in humans
- Off label human & veterinary use
- Requires carrier: collagen and ceramics commonly used
BMPs

- Veterinary case studies/series
- Dose range 0.017 to 2.1 mg/kg
- Numerous case series/reports: Mainly RHBMP-2 studies in canine long bones and mandibles for delayed/non-unions and critical sized defects.
- Schmoekel JSAP 2005: Prospective study for 41 sites for non-unions & arthrodesis in dogs & cats. 90% success rate. Historical controls.

Arzi et al 2014 – VetSurgery
BMPs – dog experimental studies

• Faria et al Vet Surg 2007
  • 21 dogs, 1mm gap tibial osteotomy with ex fix
  • Bone healing and mechanical testing improved in 0.2mg/ml group compared to 0.05mg/ml and control.

  • 27 dogs, 1mm gap tibial osteotomy with ex fix comparing 0.2mg/ml and 0.4mg/ml and controls
  • Bone healing & histology significantly improved with both groups but 0.2mg/ml was superior
BMPs – Cons in Animals

- Cost: $2500-$3500 USD
- Optimal method of delivery still unknown in small animals
- Excessive bony overgrowth can affect function, as for spinal cord impingement after vertebral stabilisation (Kirker-Head et al JAVMA 2007)
- Transient worsening of lameness was observed in a few cases after injection of rhBMP-2. (Milovancev et al Vet Surg 2007)
BMPs- Cons in humans

- Epstein 2013. Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount. Surg Neurol Int 2013;4
- Carragee et al 2011 (The Spine Journal): review of rhBMP2 studies suggest possible study design bias with industry-sponsored studies reporting 0% complications. Risk of adverse events is 10-50 times the original estimates reported in these articles
- Reported complications in humans include exuberant/ectopic bone formation, paralysis (cord, nerve damage), dural tears, bowel–bladder and sexual dysfunction, respiratory failure, inflammation of adjacent tissues, fetal developmental complications, scar, excessive bleeding and even death.
- FDA issued warning in 2008 for off label use in cervical spines
  - Another warning on increased cancer risk (3.8%) (Even et al J Am Acad Orthop Surg 2012)
Platelet rich plasma (PRP)

- Multiple growth factors within alpha granules of platelets: PDGF, TGH-beta, IGF, EGF, VEGF which are key elements in wound healing and bone healing.
- Lots of human studies (dental, cartilage, soft tissue) but insufficient evidence and high level studies to support clinical use.
- Huge variety in preparation techniques in studies. Small animal systems available commercially.
- Several small animal studies on bone healing: Clinical evidence is still lacking for use in bone healing augmentation.
Cell Based – MSCs

- Introduce MSC into the area of required new bone to allow proliferation, differentiation, produce necessary cytokines, invoke vascular response and produce matrix and new bone.
- Bone marrow MSCs extensively studied, but more recently fat MSCs.
- Strategies: Culture expansion & selective retention.
- Several studies show improved bone healing rate in MSC techniques.
- More studies required.
The future

- Continual research
- Multimodal approach, combination.
Key review papers

- Innes J. F., Myint P. Demineralised bone matrix in veterinary orthopaedics: A review. VCOT 2010;23:393-399
- Ragetly G. R., Griffon D. J. : Bone grafting techniques in small animals. VCOT 2011; 24: 1–8
- MSCs – (Equine based but good principles)
Questions?