WHITE PAPER - DRAFT

Bioactive compounds In Orthopaedics: Bridging the Gap In Broken Bones

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Executive Summary

The article gives a flavour of bioactive materials currently known or being developed for use in bone grafts, based on available material in the public domain on the internet. Four types of bioactive bone grafts are described; Factor based, cell based, ceramic and polymer based grafts. The current state of the art is that bone grafts do not yet approach the versatility of bone in terms of strength, elasticity and resistance to fracture. The field is very active in terms of ongoing research and some suggestions as to future directions are made.

Introduction

Broken bones (fractures) have been a feature of man's existence since time immemorial. There is archaeological evidence for the successful repair of broken bones by prehistoric man and ancient peoples from the Egyptians to the New World knew how to set bones proficiently.

Where there is a clean break or sufficient bone to keep in place at the fracture site with plates or screws, the natural healing process can take place. In such cases, the bone heals in the following manner: the ruptured blood vessels of the broken bone result in the formation of a blood filled swelling - a haematoma. Cartilage is then formed to replace the haematoma and this in turn is replaced by a bony callus. When the callus is subjected to physical stress, it responds by remodelling the bone and eventually forms a strong permanent patch at the site that can even be stronger than the original bone.

If there is missing bone and a gap needs to be bridged, the situation is more problematic. The ideal solution would be to assist the natural healing process to close the gap. In 1999 there were 500 000 bone grafts in US and in 9 out of 10 cases this was achieved either with grafts of bone taken from another part of the patient (autografts) or using sterilised bone from donors or cadavers (allografts). However, autografts can be limited by available material and allografts do not promote healing as well as autografts and, despite sterilisation, still bring with them a small risk of transmitting infections.

There is therefore a need for other bone grafting methods. The ideal solution would be one where the graft can still promote the natural bone repair process to ultimately produce new bone at the graft site. The term for such materials is that they are bioactive. This article will briefly cover progress.

Bioactive compounds

In 1968, Larry Hench found himself talking to an officer from MASH and first heard of the need for bone grafts to help soldiers whose bones were otherwise shattered beyond repair. Larry thought about possible materials and thought that calcium rich glass might be a suitable candidate. By 1968 he had a grant from the US military medical services which ultimately led to the birth of Bioglass. Larry is still actively finding ways to improve the successful original product even further, conducting research here in Cambridge.

Laurencin[1] and co-workers divide bioactive bone grafts into four groups as exemplified by table 1 below, Factor based, cell based, ceramic and polymer based grafts.

Table 1. Four groups of bioactive bone graft materials.

Class	Description	Examples
Factor based	Natural and recombinant growth factors used alone or in combination with other materials	TGF-beta, PDGF, FGF, BMP
Cell based	Cells used to generate new tissue alone or seeded onto a support matrix	Mesenchymal stem cells
Ceramic based	Includes calcium phosphate, calcium sulfate, and bioglass used alone or in combination	Osteograf, Norian SRS, ProOsteon, Osteoset
Polymer based	Both degradable and nondegradable polymers used alone and in combination with other materials	Cortoss, OPLA, Immix

Factor based bone grafts

The combination and simultaneous activity of many factors result in the controlled production and resorption of bone under natural conditions. These factors, residing in the extracellular matrix of bone, include TGF-beta, insulinlike growth factors I and II, PDGF, FGF, and BMPs. Researchers have been able to isolate and, in some cases, synthesize these factors. Much work has been done and research continues, with some products for clinical use appearing on the market.

Cell based bone grafts

It is possible to induce the *in vitro* differentiation of mesenchymal stem cells to create bone cells (osteoblasts) by culturing them in the presence of various additives such as dexamethasone, ascorbic acid, and glycerophosphate.

The addition of other factors such as TGF-beta and BMP-2, BMP-4, and BMP-7 to the culture media can also induce stem cells to develop into osteoblasts. In the laboratory it is possible to combine such stem cells with porous ceramics and when implanted into animals, bone growth was achieved in as little as 2 months.

One company that has capitalized on the enormous potential of mesenchymal stem cells and stem cells in general is Osiris Therapeutics, Inc. They currently have several products under development based on stem cells, with varied applications, including regeneration of new bone, cartilage, tendon, cardiac muscle, and adipose tissue.

Ceramic based bone grafts

Approximately 60% of the bone graft substitutes currently available involve ceramics, either alone or in combination with another material. These include calcium sulphate, bioactive glass and

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[1] C. T Laurencin *et al*, Bone Graft Substitute Materials. Web article. Last Updated: March 15, 2005. see http://www.emedicine.com/orthoped/topic611.htm

calcium phosphate. They often require high temperatures for scaffold formation and have brittle properties. Therefore, they are frequently combined with other materials to form a composite.

The use of ceramics, especially calcium phosphates, is driven in part because the primary inorganic component of bone is calcium hydroxyapatite (HA), a subset of the calcium phosphate group. Calcium phosphates promote the migration of bone cells to the site and can also induce bone cell differentiation.

The following material fall in this group:

- Calcium sulphate, also known as plaster of Paris. It is biocompatible, bioactive, and resorbable after 30-60 days. Significant loss of its mechanical properties occurs upon its degradation and therefore it is not a material of choice for load-bearing applications.

- Osteoset (Wright Medical Technology, Inc) is a tablet for use for filling in defects that is degraded in approximately 60 days.

- AlloMatrix is Osteoset combined with demineralised bone matrix to form a putty or injectable paste.

- Bioactive glass (bioglass) is a biologically active silicate-based glass (Novabone). Its high modulus and brittle nature make its applications limited, but it has been used in combination with polymethylmethacrylate to form bioactive bone cement. It is used with metal implants as a coating to form a calcium-deficient carbonated calcium phosphate layer which facilitates the chemical bonding of the implant to surrounding bone. Products include BioGran (developed by Orthovita and licensed to 3i, Inc) and PerioGlas (US Biomaterials, Inc).

- Calcium phosphates account for most ceramic-based bone graft substitutes currently available. Several types of calcium phosphates exist, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite, available in pastes, putties, solid matrices, and granules. Such products include BioOss, Vitoss & ProOsteon. However, like many of the solid calcium phosphates, they can be brittle and not suitable for use in load-bearing sites.

Polymer-based bone graft substitutes

Polymers present some options that the other groups do not, as many polymers that are potential candidates for bone graft substitutes represent different physical, mechanical, and chemical properties. The polymers can be loosely divided into natural polymers and synthetic polymers which in turn, can be divided further into degradable and non-degradable types.

Polymer-based bone graft substitutes include the following:

- Healos - a polymer-ceramic composite from Orquest, consisting of collagen fibers coated with hydroxyapatite and used for spinal fusions.
- Cortoss from Orthovita, Inc, is an injectable resin-based product suitable for load-bearing sites.
- Rhakoss, from Orthovita, Inc, is a resin composite in various forms and applied to spinal applications.
- The company Inion is also active in the area.

The advantage of degradable synthetic polymers is that they are resorbed by the body, allowing it to completely heal itself with no foreign bodies remaining. Companies have used degradable polymers such as polylactic acid and poly(lactic-co-glycolic acid) as stand-alone devices and as extenders to autografts and allografts. Two companies in this area are Bone Tec, Inc and OsteoBiologics, Inc.

New materials and approaches

Despite the many advances in bone graft substitutes, new materials and approaches to bone healing continue to be investigated. The ideal is to provide a resorbable bone graft that leaves healthy natural bone with the required structural strength and elasticity.

Whilst individual laboratories may still be pursuing one or the other preferred material or approach, surely the future lies with an integrated approach, combining engineering and bioactive structural surfaces, the infiltration or induction of new bone cells by suitable cell signals followed by graft resorbtion and bone remodelling.

Laurencin laboratories already suggest that they are taking such an approach, based on a microsphere-based design. Laurencin *et al* have created a porous biomimetic matrix that provides an osteoconductive surface for osteoblast attachment and an interconnected pore system to allow cellular proliferation and migration. This basic design has also been combined with a ceramic to form a composite matrix.

Perhaps in the future we will see patients fitted with composite bone grafts, where a structural component provides initial strength to allow the patient to recover mobility. A linked secondary matrix promotes the invasion and induction of osteoblasts as an inner or outer shell. One might envisage the resorbtion rate of the structural component to be tailored to allow a gradual increase in stress on the newly forming bone to allow a seamless transition of load transference and increased strength to the regenerating material, until remodelling finally results in a completed bone with no evidence of damage or artificial agents.

Appendix

An example of references found on PubMed 1999 – 2005. Other relevant articles were also found on the web and a search on the patent database esp@cenet found 338 patent titles using the keywords Bone and bioactive. For brevity, only the PubMed references are included here.

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