Clinical Application of Resorbable Polymers in Guided Bone Regeneration

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Summary: Guided bone regeneration was shown to be successful *in vitro* and *in vivo* using resorbable or nonresorbable materials. Resorbable material has the advantage of progressive substitution by bone. Resorbable polymers of α-hydroxy acids like polylactide or polyglycolide are commonly used for tissue engineering and in guided bone regeneration. In clinical studies, guided bone regeneration was successful in non-weight bearing bone, e.g. in dental surgery and craniofacial surgery. This paper reports the preliminary result of using resorbable poly(L/DL-lactide) 80/20% scaffolds in weight bearing bone with infected large segmental defects as well as in small bony defects of hand due to benign tumour, bone graft donor sites and as an adjunct for joint fusion. Resorbable polylactide implants were used in the form of membranes, large 3-D sponges, chips or as injectable paste. Implants were impregnated with marrow blood to add an osteoinductive component. Long-term follow up revealed that these implants are promising candidates for bone graft substitutes.

Keywords: bioresorbable polymers; clinical applications; guided bone regeneration; polylactides; tissue engineering

Introduction

Bone defects, which exceed ''critical size'', do not heal spontaneously. In general, autogenous bone graft is used to promote healing of such defects. Autograft contains osteoblasts, stems cells, extracellular matrix, growth factors and cytokines, i.e. has osteogenic, osteoinductive and osteoconducitve properties. Osteoblasts in the autograft lay down osteoid matrix and express osteogenic growth factors. These molecules induce the migration, proliferation and differentiation of progenitor cells into osteoblasts. Stems cells are able to divide and differentiate towards osteogenic lineage in an appropriate microenvironment. Extracellular matrix serves as a scaffold for cells. This complicated cascade of events finally leads to bone healing.

Although autograft is the ''gold standard'', it is limited in supply. Graft harvesting is associated with events such as donor site morbidity, bleeding and nerve injury, to mention but a few.

Hence, there is a demand for new bone graft substitutes, which may promote bone regeneration. Such a substitute would simulate the autograft, that is, it would be osteogenic, osteoinductive and osteoconductive.

Numerous studies have been carried out *in vitro* and *in vivo* to find an ideal implant and identify suitable conditions for guided bone regeneration.[1–6] The success of such implants depends on at least three factors: exclusion of unwanted tissues and cells from the defect, providing the space for newly formed bone, and maintaining autogenous growth factors within the healing area.[4] Autogenous cells seeded to the implants and/or growth factors added to the scaffolds may facilitate bone regeneration.

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Various resorbable and nonresorbable materials of organic or inorganic origin in a variety of geometrical forms such as microspheres, granules and/or sponges were successfully used to achieve guided bone regeneration in various animal models. Resorbable materials have an advantage over nonresorbable ones as they are progressively replaced by host bone and there is no need for removal.

Polyhydroxyacids occupy an important position among the resorbable polymers used in guided bone regeneration. As a result of successful use of these polymers for bone regeneration in animals, they were also tried clinically in humans. Primary applications were in dentistry, cranio-maxillofacial surgery and pediatric surgery. In weight bearing bone, resorbable polymers may play a role in guided bone regeneration if bone stability is ensured by other means of fixation. Resorbable polymeric scaffolds can be used in simple bone grafting, in the treatment of segmental bone defects, delayed union and nonunion, joint fusion, osteoporosis related fractures and in the correction of congenital bone defects.

This paper reports on the long term clinical use of microporous membranes, sponges or chips from poly(L/DL-lactide) 80/20% for the management of various bone defects in a limited number of patients.

Material and Methods

Implants

Microporous membranes and sponges were prepared from poly(L/DL-lactide) 80/20% with a molecular weight of 200.000 dalton purchased from PURAC Biochem, Gorinchem, the Netherlands. The techniques for the preparation of membranes and sponges have been described elsewhere.[7,8]

Patients

There were 12 patients treated with resorbable implants as a sole treatment or as an adjunct to the treatment. The cases treated are listed in Table 1.

Results

Compound Bone Fractures with an Acute Infection

Two cases of compound bone fractures with an acute infection were stabilized using metallic implants. To control infection, the polylactide scaffolds were impregnated with an antibiotic and used as carriers for local delivery of the drug. As the scaffolds were removed during the second debridement, no long-term results of this study are available.

Long Segmental Defect

A free vascularized fibular graft and a massive allograft were used as a limb salvage procedure in the treatment of a 24 cm long segmental defect resulting from osteogenic sarcoma in the left distal femur of a 14-year old boy. The operation was complicated by bone infection and soft tissue necrosis. The resorbable polylactide scaffold soaked with an antibiotic and marrow blood was used as an adjunct to deliver antibiotics and for guided bone regeneration (Figure 1).

Table 1.
Clinical cases treated with resorbable polylactide implants.

Diagnosis	No. of cases	Indication
Acute compound fractures	2	As antibiotic carriers
Osteogenic sarcoma	1	Guided bone regeneration, as antibiotic carrier
Osteomyelitis in proximal femur with segmental defect	2	Guided bone regeneration as antibiotic carriers
Fungal osteomylelitis in carpus	1	Chip graft for joint fusion
Nonunion of previous knee fusion	1	Chip graft for joint fusion
Iliac bone graft for ankle joint fusion	1	Guided bone regeneration of bone graft site
Enchondroma in hand	4	Chip graft for bone defect, no donor site required

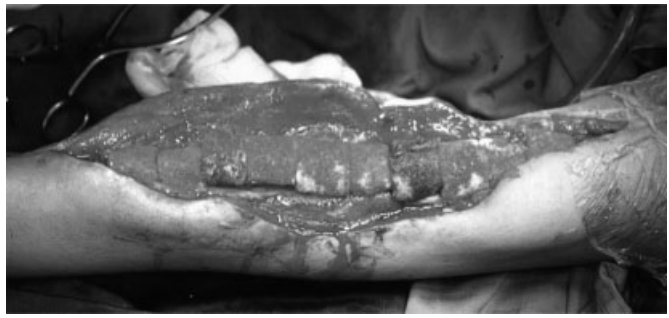

Figure 1.
Surgical procedure to salvage the limb. Polylacide scaffolds were used as an adjunct to free vascularized graft and allograft to deliver antibiotic and guide new bone.

Three years after surgery not much new bone had formed in the defect as revealed by radiological evaluation (Figue 2).

There are a few possible reasons for unsuccessful guided bone regeneration. For example, the early generation of polylactide scaffolds was brittle, the bone defect was very long, the marrow blood did not completely penetrate the whole scaffold, which resulted in a low number of osteoblasts and stem cells present in the scaffold. On the other hand, it can also be argued that such long bone defects require the use of vascularized bone graft to heal.

Long Segmental Defect and Osteomyelitis in Proximal Femur

A right trochanteric hip fracture in an 85-year-old women was fixed with a dynamic hip screw. Two months latter, she slipped, fell, and sustained a new fracture distal to the implant. An additional complication was osteomyelitis. Bone debridement resulted in a 6 cm long segmental defect. The bone was stabilized with an intramedullary nail and the defect was treated with a polylactide scaffold impregnated with Vancomycin and marrow blood. The scaffold were surrounded with a perforated polylactide membrane to enhance its resistance to muscle pressure (Figure 3–6).

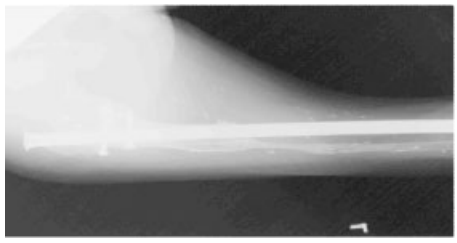

Figure 2.
X-ray image of implantation site 3 years post-surgery.

Early X-ray scans revealed some bone bridging in the defect. To hasten bone regeneration, the chips cut from the polylactide sponges were soaked with marrow blood and injected twice into the defect under fluoroscopic control (Figure 6).

There was progressive bone healing and the patient was able to walk with a moderate support. The X-ray images at 8 years revealed remodeled bone over the medial wall of the bone defect although bone regeneration of lateral wall was incomplete (Figure 7).

A 50-year-old female with diabetes mellitus, septicaemia and osteomyelitis of right proximal femur suffered from a pathological fracture at the infection site. After thorough debridement of the osteomyelitis, the remaining 5 cm long bone defect was stabilized with an intramedullary nail. The defect was filled with the polylactide scaffolds soaked in iliac crest marrow blood. The X-ray images at four and half year revealed good regeneration of bone in the defect (Figure 8). The patient was able to walk unaided.

Fungal Osteomyelitis in the Carpus

A 40-year-old woman had a 25 year history of fungal osteomyelitis of the right carpal

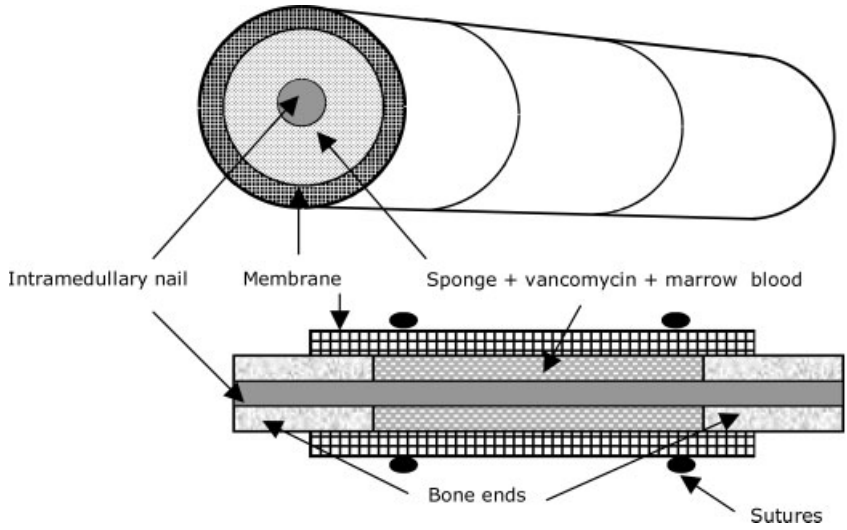

Figure 3.
Schematic illustration of the treatment of a segmental bone defect with polylactide implants.

Figure 4.
A. Polylactide sponges impregnated with vancomycin; B. Marrow blood is harvested from the iliac crest; C. Sponges are impregnated with marrow blood.

bone. After debridement of the radial side of the carpus, a cancellous bone graft taken from the radial styloid was used for partial wrist fusion. Since a large large amount of bone graft would have to be used to promote bone healing in the defect, the chips cut from the polylactide scaffold were soaked with marrow blood and applied to the fusion site to hasten the healing and minimize donor site morbidity. At 8 weeks, a good fusion mass was seen in the X-ray images (Figure 9).

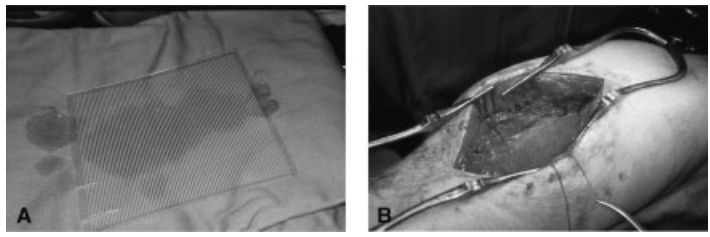

Figure 5.
A. Perforated polylactide membrane; B. Membrane is placed under the intramedullary nail.

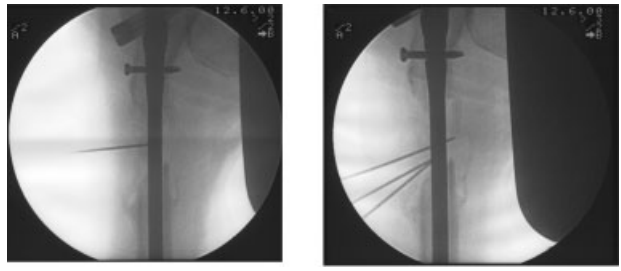

Figure 6.
X-ray images show some bone bridging in the defects. The polylactide chips soaked with marrow blood were injected into the defect site to hasten bone regeneration.

Nonunion of the Previous Fusion Site

A 60-year-old man with gouty arthritis had a fusion operation on the left knee 20 years before the present admittance to the hospital. The medical investigation revealed persistent nonunion of the fusion site and unstable knee which was accompanied by pain. Revision fusion was performed using cancellous bone graft mixed with chips cut from a polylactide sponge. This treatment hastened bone union (Figure 10).

Treatment of the Donor Site after Harvesting of Cortico-Cancellous Bone Graft from the Iliac Crest

A 30-year-old man with nonunion following an ankle fusion procedure underwent fusion revision using cartico-cancellous graft from the iliac crest. The donor site was implanted with the polylactide scaffold. Seven months after the operation the donor site was healed with new bone (Figure 11).

Enchondromata of Phalanges and Metacarpals in Hand

Four patients with enchondromata benign tumour were treated with curettage. The patients preferred not to use autogenous bone graft to promote bone healing in the defects. Consequently, chips cut from a

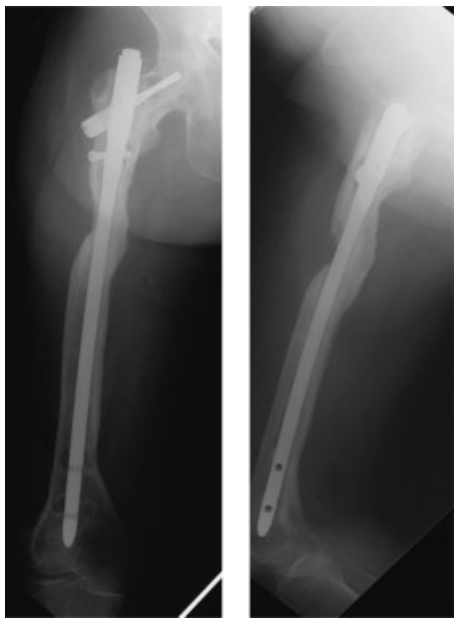

Figure 7.
X-ray images of the same patients 8 years postoperation.

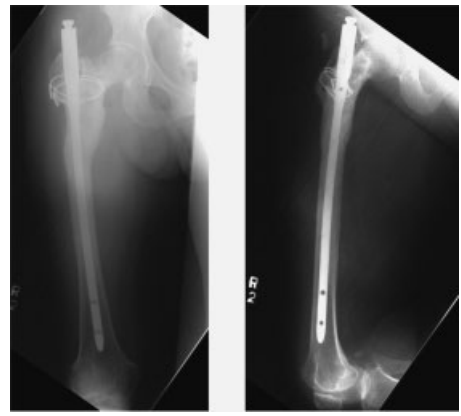

Figure 8.
X-ray images of the operated site 4.5 years postoperatively.

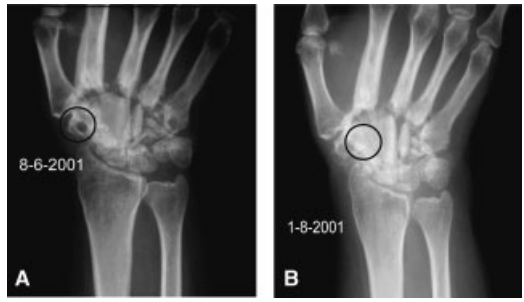

Figure 9.
X-ray images of the right carpal bone. A. Bone defect at the time of operation; B. Defect treated with autogenous bone graft and chips of polylactide sponge impregnated with marrow blood 8 weeks post-surgery. Note good fusion mass.

polylactide sponge soaked with marrow blood aspirated from the radial styloid were used to pack bone defects. Long-term X-ray evaluation revealed progressive bone healing with no recurrence of the tumour. Bone regeneration seemed to proceed slower, however, than in the case when defects were packed with cancellous bone graft (Figure 12).

Discussion

Resorbable polymers have been studied extensively as candidates for bone tissue engineering. Both, *in vitro* and *in vivo* studies in animals[7] confirmed that these polymers can provide a microenvironment for proliferation of osteogenic cells and expression of osteoblastic phenotype. It has been appreciated, however, that it may not be possible to extrapolate the results of animal studies to human situations.[11] Clinically, membranes from resorbable polymers were used for guided bone regeneration in dental surgery. Functional outcomes were good.[1–4,10,12,14] The membrane acted as a barrier protecting the healing site from invasion by fibroblast. Adding BMP or bone matrix to resorbable scaffolds enhanced guided bone regeneration.[6,9] In craniofacial surgery, resorb able polymeric scaffolds play an important role in guided bone regeneration.[5] Resorbable polymers have also been used successfully to replace bone graft in spinal fusion.[13] In the present study resorbable porous polylactide scaffolds had successfully replaced a vascularized bone graft procedure in an 85-year-old patient with

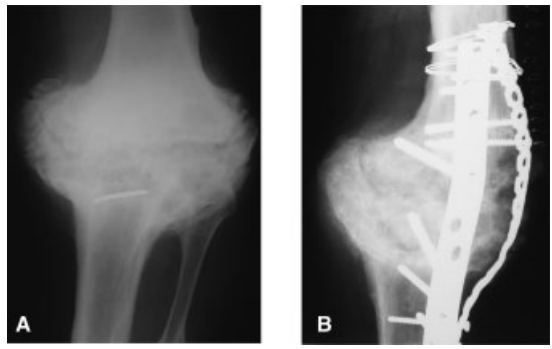

Figure 10.
X-ray images of the knee. A. Nonunion of the fusion site at the time of admittance to the hospital; B. Cancellous bone graft mixed with chips cut from polylactide sponge hastened bone union.

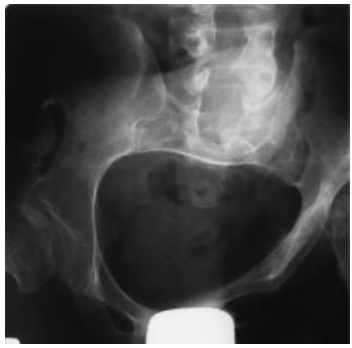

Figure 11.
X-ray images of the donor site implanted the polylactide scaffold 7 months postoperatively. The site has healed with new bone.

long segmental bone loss in an infected proximal femur. Successful guided bone regeneration minimized the morbidity of the donor site and simplified the surgical procedure.

Resorbable scaffolds from poly(L/DL-lactide) 80/20% have also proved to be functional in the treatment of small bone defects, joint fusion and the treatment of nonunion. The use of the scaffolds simplified the treatment procedures and reduced the morbidity associated with harvesting of bone graft. Impregnation of the scaffolds with marrow blood containing stem cells and osteoblasts increased the osteoinductive potential of the scaffold. Although the number of cells present in the scaffolds after impregnation is expected to be low, this is a simple and inexpensive *in vivo* procedure of tissue engineering. On site centrifugation of marrow blood may increase the number of active cells present in the scaffolds. The combination in the present study of the polylactide sponge with the perforated membrane may provide an optimal environment for bone regeneration by allowing for attachment and proliferation of osteogenic cells and for neovascularization.

The drawback of the present study was poor mechanical properties of the polylactide sponges. This problem was solved, however, by modifying the production technology which provides the sponges with enhanced mechanical properties. Adding nanosize hydroxyapatite ceramics to the polymer system also enhanced the scaffolds osteoconductive potential.

The use of implants consisting of polylactide scaffolds seeded with autogenous stem cells might enhance their regenerative potential. As the time factor plays an important role in clinical practice, it might be advantageous to use stem cells harvested from abundant adipose tissue rather than from bone marrow. Another treatment modality to promote the attachment, growth and activity of osteogenic cells on polylactide scaffolds might be the treatment with low temperature radio frequency plasmas.[7]

Conclusions

The results generated by the present studies showed that resorbable polylactide scaffolds are functional in the treatment of small and large bone defects irrespective of the fact that all the clinical cases treated

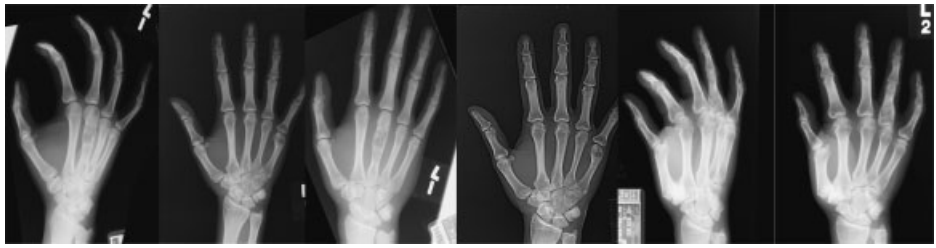

Figure 12.
X-ray images of the enchondromata of phalanges and metacarpals in hand treated with curettage. Bone defects were treated with the polylactide sponge impregnated with marrow blood. Note progressive bone healing with no recurrence of the tumour.

were difficult. The scaffolds can be used alone, together with autogenous bone marrow or in combination with bone graft. An additional advantage of using scaffolds is that it minimizes the amount of autograft that needs to be harvested. The scaffolds can also serve as drug carriers. The delivering of antibiotics to the infected operation site serves as an example.

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