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Interface reactions between biodegradable implants and avascular bone grafts or vascular host site in the porcine skull

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Poly-L-lactide (PLLA) threaded pins and polydioxanon (PDS) woven bands were used to stabilize bone fragments in the reconstruction of the calvaria of 27 minipigs. The aim of the present study was to determine whether the rate of degradation of resorbable implants is low enough to maintain fixation until the bone has united and, at the same time, high enough to ensure that the implant material loses its strength and no longer interferes with bone growth and remodelling. The experiment lasted between 1 and 24 weeks. Staining *in vivo* and radiographs were performed throughout the experiment. The treated calvaria were cut into thin sections and examined microradiographically and histologically. The results confirmed that the form of the skull could be sufficiently maintained in the animal experiment over the given periods to warrant the use of such fixations in craniofacial surgery. The use of degradable material could eliminate the possible need for a second operation to remove implants and would reduce interference with the growth process.

1. Introduction

In craniofacial surgery in children it is common practice for metal implants such as plates, screws and wires to be used for the fixation of fragments of the skull. The indications are congenital growth deformities such as premature stenosis, Morbus Crouzon, Morbus Apert, plagiocephalus, trigonocephalus, etc. and large congenital bony defects, for example, occipital encephalocele or due to trauma following treatment of subdural and epidural haematoma.

Growth, which is obviously a very significant factor in paediatric surgery, must be taken into consideration in the treatment of the craniofacial skeleton, especially in small children. The weight of a neonate brain at full-term is approximately 330 g; it triples by the end of the second year of life. According to Coppoletta and Wollbach [1], the contents of the skull reaches 80% of its final volume by this time and only increases another 20% by the time the child is 10–12 years of age.

The application of implants in this phase of intensive growth may lead to complications. Due to the massive changes taking place in the formation of the skull and mechanical interference of the implants with the galea, postoperative decubitus and ulceration is not uncommon however carefully the implants have been inserted. The implants are often undesirable for functional or cosmetic reasons (e.g. hairdressing) and remodelling processes such as drift phenomena may even lead to intracranial displacement of the implants. The implants have to be removed to avoid such complications and this necessitates a second operation. In addition, the screws and cerclage wires often do not hold well in the paper-thin bone of the calvaria.

The use of biodegradable fixation devices may help to circumvent these difficulties. Experience with biodegradable implants has already been gained and they have been used successfully in human medicine [2–7]. The results seem to indicate that the resorbable implants are equally as efficient as their metal counterparts.

2. Materials and methods

2.1. PLLA and PDS materials

The implant set consists of PLLA threaded pins, PLLA nuts and PDS woven bands (Fig. 1). The PLLA used was a pure crystalline 1-1-PLLA (poly-L-lactide, Boehringer Ingelheim Ltd, FRG) with an average molecular weight of 220 000–500 000 IU. The molecular weight given is the viscosity-average molecular weight M_v calculated from the Mark–Houwink equation using the following constants: $K = 5.45 \times 10^{-4}$ dL/g and $\alpha = 0.73$. The mechanical properties determined using samples of this material were as follows: tensile strength = 55 N/mm^2; compressive strength = 110 N/mm^2; bending strength = 120 N/mm^2; E-modulus = 4000 N/mm^2 (data from Mathys Foundation, CH-2544 Bettlach).

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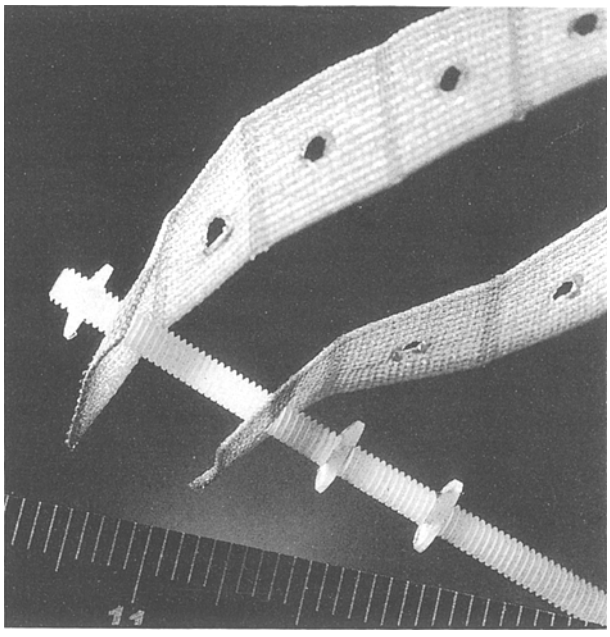

Figure 1 Threaded rods and nuts (PLLA) and woven bands (PDS) used for fixation of the bone grafts.

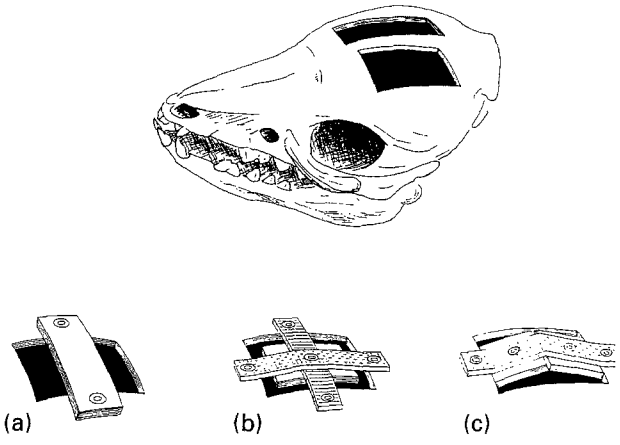

Figure 2 Bone defect in the cranial vault and different grafting procedures: (a) fixation of bony bridge to the cranial vault with threaded rods; (b) floating osteoplasty; (c) tent-like bone bridge fixed with a PDS tension band.

The PLLA threaded pins had a metric thread with an outer diameter of 2.5 mm (M2.5). The PLLA nuts (M2.5) had an outer diameter of 5.0 mm and a peripheric four-hole drive. The nuts serve to protect the adjacent soft tissues and were of 1.0 mm maximum thickness. The threads were machined using a cutting tool (Mathys Ltd., Bettlach, Switzerland).

The degradable Ethicon^R woven bands were 10 mm wide and 0.5 mm thick (Johnson & Johnson, Ltd.). These are manufactured from PDS, a commonly used suture material. Their maximum tensile strength was 88 N.

2.2. Experimental design

To obtain a good basis for comparison, especially with regard to the growth rate, 6-week-old, weaned Göttinger minipigs were selected for the experimental study.

The operation procedure was identical for all 27 animals, namely, excision of two windows in the temporoparietal bone (left: 20 mm × 30 mm; right: 15 mm × 40 mm), however, the reconstruction procedures to cover the resected skull differed:

1. fixation of a bony bridge to the cranial vault with threaded rods only (Fig. 2a);
2. floating osteoplasty without direct contact of the vascularized host bone with the avascular bone graft (Fig. 2b);
3. a tent-like placement of the fragments, the latter fixed by a combination of woven bands and rods (Fig. 2c) [9];
4. modifications of 1–3;
5. no reconstruction of the defect.

54 defects were created in the cranial vault of the 27 minipigs; the type of reconstruction and associated duration of the experiment are shown in Table I.

In order to assess the results of this study, the first three procedures were grouped for comparative analysis. The modifications served to explore the limits of this operative procedure and are not specifically addressed in this paper. Those defects which were not reconstructed were observed and assessed clinically and compared with the reconstructed sites.

2.3. Assessment and evaluation

To follow the progress of the experiment, the animals were sedated and anteroposterior radiographs were made every 2 weeks. At the same time, intravital polychrome labelling [8] was administered so that the dynamic process of remodelling could be assessed.

Following euthanasia, the calvaria were embedded in methylmethacrylate and cut into 500 μm undecalcified sections using a Leitz saw microtome.

On the basis of radiographs of the 500 μm sections, those specimens containing parts of screws were selected to be ground down to 50–70 μm. These thin

TABLE I Relationship between defect type and number, and experiment duration

Reconstruction procedure	Number of defects with experiment duration (weeks)								
	1	2	3	4	5	6	8	16	24
1 Bone-to-bone rod fixation	1	1					2	2	3
2 Floating osteoplasty			1	1	1	1	1		2
3 Tent-like fragment placement			1	1	1	1	1		2
4 Modification of the above							3	4	1
5 No reconstruction	1	1	2			2	5	8	4

sections could then be evaluated using fluorescence and polarization microscopes before being Giemsa stained.

3. Results

None of the 27 animals treated showed signs of systemic infection or meningitis/encephalitis at any time during the experiment.

In six minipigs, wound dehiscence with abscess formation in the area of the cranioplasty was observed. The infections were healed by local antibiotic irrigation, nonetheless three cranioplasties had to be removed.

At 6 weeks the neurocranium was of the following average dimensions: length 60 mm; width 45 mm; base of the skull to the crown 30 mm. At the end of the maximum experimental period of 6 months the dimensions were: length 110 mm; width 80 mm; base of the skull to the crown 55 mm. In this period of rapid growth, it becomes apparent after only a few weeks that the pins and woven bands will eventually be surrounded by bone due to the drift phenomenon. This phenomenon also led to a relative displacement of the implants towards the cranial cavity (Fig. 3).

Whether the grafts are stably fixed (Fig. 2a) or floating (Fig. 2b), regenerated bone can be observed after 4–8 weeks at the vascularized resection margins of the host and on the edge of the initially avascular replanted cranial grafts. A prerequisite of remodelling is functional circulation. In the course of the following weeks, the grafts were revascularized, partially resorbed and remodelled and almost completely reintegrated after 4–6 months (Fig. 4).

The grafts showed more intense resorption than the host sites, especially before months 2–4. Histologically, this led to temporary loosening of the screw anchorage; later on, new bone formed at the interface (Fig. 5).

Parallel to bone regeneration, the implants start to show increasing signs of fissures and fragmentation after the second month. Only after 4 months can intracellular particles, which have the same refraction as PLA and PDS, be recognized in polarized light. Connective tissue and old or newly formed bone was observed in close contact with the screw. After the second month, an increasing number of fissures appeared in the implants (Fig. 6). At no time did signs of inflammation or round cell infiltration become apparent (Fig. 7a, b).

For those calvarial defects which were reconstructed, bone consolidation could be clearly seen after 6–8 weeks. The type of bone graft, whether stable or unattached does not seem to have any significant influence on the rate of bone regrowth. Those calvarial defects at the donor site which had not been reconstructed showed signs of radiologically visible, though extremely thin, bone only after 2 months at the earliest. Reconstructions which protrude above the level of the cranial vault will be integrated into the normal shape of the head during growth so that there is no noticeable deformation after 6 months. The grafts undergo considerable resorption and remodelling in the first 6 weeks. During this period, intensive bone regeneration can be observed at the

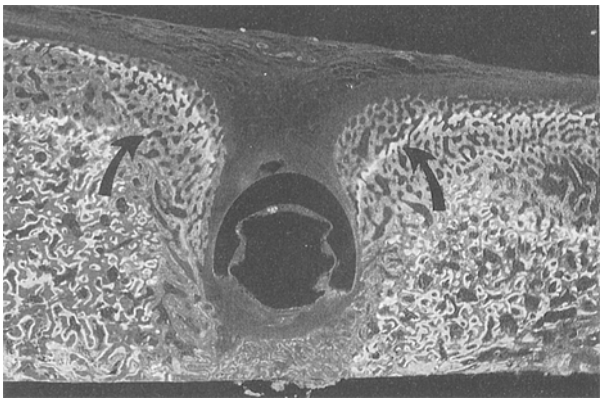

Figure 3 Drift phenomena in the vicinity of a PLLA screw at the host site: bone starting to grow around the screw (arrows). This led to a relative migration of the implants towards the cranial cavity (6 weeks).

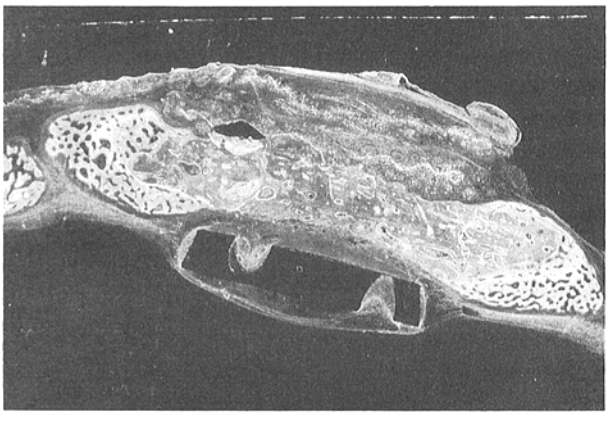

Figure 4 Bone reaction in a graft at 2 months. Two woven bands cross the top of the graft. The nut lies below the graft. The avascular bone graft revascularized within 4 weeks and a bony bridge on both sides was built. Within the graft remodelling has started, new bone formation is seen in the gap between graft and host site (both start approximately 4 weeks post-op.).

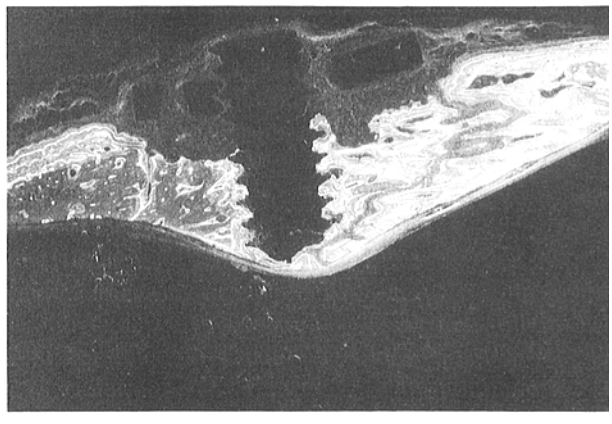

Figure 5 Bone reaction underneath an anchoring site. Same screw as in Fig. 6. Resorption becomes visible under the PDS bands. Around the screw, bone formation and remodelling activity has been taking place for the last 4–6 weeks. Bone is in close contact with the implant. Drift has also started on the sides of the bands (4 months).

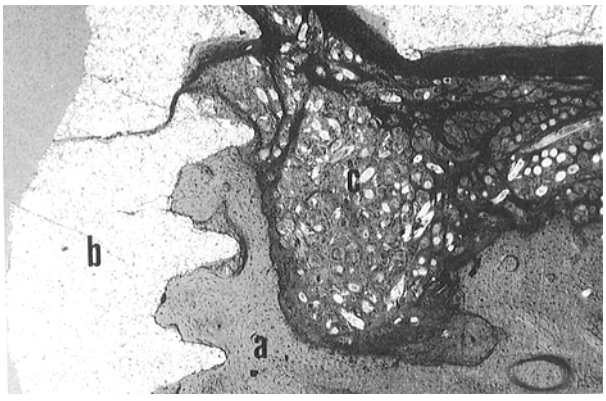

Figure 6 Anchoring of the woven band in the host bone. The polarized light especially highlights the polymer implants. Close contact between bone and PLLA screws is found. Fragmentation of the polymer has occurred and fissures are invaded by soft tissue (a. bone; b. PLLA; c. PDS fibres of the woven band) (4 months).

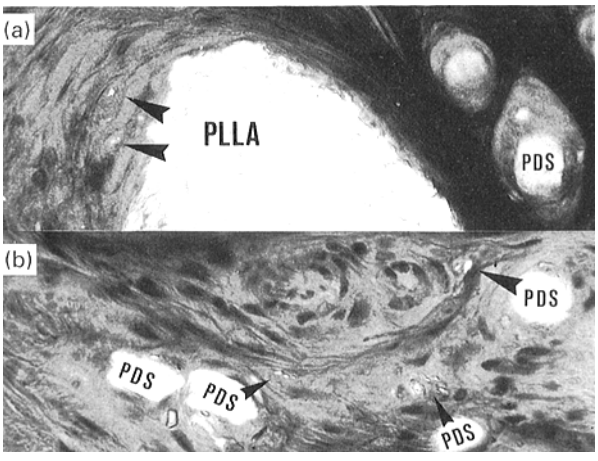

Figure 7 (a) PLLA degradation and phagocytosis. The implant surface is roughened, small particles in the close vicinity of the PLLA rod are phagocytosed (4 months). (b) Phagocytosis in the vicinity of PDS fibres of the woven band. Connective tissue forms between the PDS fibres. Various cells contain small polymer particles (4 months).

margins of the graft and at the margins of the replanted calvarial segment. These initially avascular grafts are progressively revascularized during the following weeks and by the fourth month they are completely integrated into the adjacent bone.

4. Discussion

The 6-week-old, weaned minipigs did not present any adverse reactions to treatment with biodegradable implants in the cranial vault. The rapid growth of the neurocranium between the second and eighth months can be compared with the massive increase in volume of the child's brain between birth and the second year of life. This period is clinically relevant since congenital deformities often become manifest during growth and should be corrected by operative intervention as soon as possible to ensure the best prognosis.

The biodegradable material was well tolerated in general. The relatively high infection rate in the animal experiment (6 of 27 animals) cannot necessarily be attributed to the resorbable material or to the operative procedure but should be seen in the context of animal behaviour. The animals were in direct contact with dirt and with each other, occasionally biting each other in play. The risk of infection could be reduced by treatment with systemic antibiotics and by keeping the animals in separate pens, if possible on a platform to avoid contact with the ground. Both these measures would, however, be an additional stress factor for the animals and go against their natural herd instinct. The implants had to be removed from three animals [9].

In this experiment, the reconstruction sites obviously remained clinically stable throughout. The woven bands and screws were surrounded by bone within only 6–8 weeks. The additional support provided by the regenerated bone at the resection margins supplements the initial stabilization of the implants and replaces it within a short time. Once the bone takes over the stabilizing function, the implant becomes redundant.

Fissures and fragmentation visible after 2 months seem to indicate the commencement of implant degradation. In these areas, in which a high concentration of low molecular degradation products are to be expected, neither sequestrations nor any other adverse reactions were observed. Our results confirm the findings of Vert [7] that PLA implants are not resorbed after 6 months. The question of how long it takes for the material to disappear completely cannot be answered by this study.

5. Conclusions

The results of this experiment demonstrate that 6 months is a sufficient period for the incorporation of non-vascularized grafts to take place. Osteoplastic reconstruction with the aid of implants leads to a more rapid consolidation than leaving the defect open. In craniofacial surgery, the following must be considered: the more extensive the osteoplasty, the more important it is to achieve adequate coverage and function. This is especially relevant during growth since large open areas of the cranial vault or unstable fixation of the osteoplasty could lead to deformities due to intracranial pressure. The rate of degradation does not appear to be detrimental to the growth of the cranial vault. The complete disintegration of the implant material appears to be too slow to guarantee that no fragments will be displaced into the cranial cavity by bone drift as occurs in a growing individual. It is to be expected that the implant material will completely disappear anyway and thus the risk of displaced fragments is not as great as for metallic implants.

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