Biodegradable semirigid plate and miniscrew fixation compared with rigid titanium fixation in experimental calvarial osteotomy

HILKKA H. PELTONIEMI, M.D., RIITTA-MARI TULAMO, D.V.M., PH.D., TERTTU TOIVonen, M.D., DORRIT HALlikainen, M.D., PH.D., PErtti TÖRMÄLÄ, PH.D., AND TIMO WARIS, M.D., PH.D.

Department of Surgery, University of Helsinki, Helsinki, Finland; Faculty of Veterinary Medicine, Department of Clinical Veterinary Sciences, University of Helsinki, Helsinki, Finland; Kymenlaakso Central Hospital, Kotka, Finland; Department of Radiology, Helsinki University Central Hospital, Helsinki, Finland; Institute of Biomaterials, Tampere University of Technology, Tampere, Finland; and Department of Surgery, Division of Plastic Surgery, Oulu University Central Hospital, Oulu, Finland

Object. To determine the biocompatibility and suitability of resorbable plates and miniscrews, consolidation of symmetrical, bilateral frontal bone craniotomies that had been closed using various methods was studied in 20 growing lambs.

Methods. Bone fixation with a flexible, punched polylactide plate and four slowly degradable, self-reinforced polyevolactide (SR-PLLA) or rapidly degradable, self-reinforced polyglycolide (SR-PGA) miniscrews (10 animals in each group) was compared intraindividually with rigid fixation by using a titanium miniplate and four miniscrews. Plain x-ray films, magnetic resonance images, histological studies, and histomorphometric studies were obtained at 4 to 104 weeks.

Conclusions. No dislocation, instability, clinical foreign body reactions, infections, or loss of fixation were observed. Bone consolidation of the 2.35-mm-wide craniotomy lines was incomplete; connective tissue–filled defects through the bone were observed in 13 of 28 lines at 26 to 52 weeks. Statistical analyses based on histomorphometric studies showed no difference in consolidation with SR-PLLA miniscrew and titanium plate/screw fixation or between the two resorbable fixation methods. Fixation with rapidly degradable SR-PGA miniscrews resulted in less effective consolidation than on the contralateral titanium-treated side (p < 0.05), but the bone segment was thicker (p < 0.005). The SR-PGA miniscrews had disappeared by 6 weeks, the polyactide plate by 104 weeks, and the SR-PLLA miniscrews had been mostly resorbed at 104 weeks. Passive translocation of the titanium plates and screws into the bone tissue was seen at 52 and 104 weeks. In rapidly growing lamb frontal bone, comparable consolidation results, without complications, can be achieved with semirigid resorbable fixation compared with rigid metallic fixation.

KEY WORDS • biodegradable plate • polylactide • polyglycolide • craniofacial surgery • sheep

The potential risks associated with metallic mini- and microfixation devices used in pediatric craniofacial surgery have given rise to the development of biodegradable minioseosthesis devices. Unless the metallic devices are removed, local restriction leading to growth alterations and their translocation inside the growing skull have been reported.8,12,18,26,30,31,44 Metallic devices also interfere with radiological studies used in patient follow up.1,4,7,9,10,14

Biodegradable polyester implants made of polylactide (PLA), polyglycolide (PGA), their copolymers, or polydioxanone have been used clinically in craniofacial surgery during the past 10 years.5,6,13,20,17,40,44 Mechanically stronger self-reinforced (SR) PLA implants have been used in congenital craniofacial malformations (T Waris, unpublished data) and in adult mandibular and maxillary corrections.11,16 The changeover to biodegradable fixation in nonloaded osteosyntheses in the infant neurocranium has been rapid.

Consolidation of craniotomy lines and small bone defects in infants has been commonly considered to be fast and effective because of the osteogenicity of infant dura. However, lack of ossification in infant neurocranium has been reported, especially with nonrigid, resorbable fixation.32 In our previous study in older sheep, covering of craniotomy lines with a wide, protecting resorbable SR-polyevolactide (PLLA) plate resulted in superior consolidation compared with that observed after placement of narrow titanium plates.27,29

The aim of this experiment was to study the biocompatibility and suitability of flexible, membranelike poly-LDL-lactide (PDLLA) plates, fixed with slowly degrading SR-PLLA or quickly degrading SR-PGA miniscrews, in unstable frontal bone osteotomies of rapidly growing lambs, using rigid titanium miniplate and screw fixation as a reference. The analysis was performed with special attention given to the consolidation pattern.
Semirigid biodegradable and rigid titanium plate fixation

Materials and Methods

This experimental study was approved by The Research Animal Commission of the Faculty of Veterinary Medicine, University of Helsinki, and by The Provincial Administrative Board, according to Finnish law.

Implanted Devices

The PDLLA plates were composed of 96% L- and 4% D-lactide, processed by compression molding and sterilized using gamma radiation (2.5 Mrad). The 0.4-mm-thick, transparent, flexible, punched plates were cut with scissors into 20 × 30-mm rectangles at surgery. The 2-mm-diameter SR miniscrews were equipped with cross-heads. The thread length (6–10 mm) was easily shortened with an oscillating saw or hot wire loop before or after insertion, and a special tapping instrument was used for the biodegradable screws. Four-hole titanium miniplates (0.6 × 4 × 25 mm) and self-tapping titanium miniscrews (3–5 mm long, 1.5 mm diameter) were used on the contralateral side.

Operative Procedure

Lams were chosen because the size, thickness, and growth pattern of the membranous bones of their skulls are comparable with those of growing human skulls. The Finnish Landrace sheep used in this study grow slowly and when mature may weigh as much as 80 kg. Twenty clinically healthy skeletal immature 4- to 7-month-old sheep weighed 22 to 32 kg (mean 25.6 kg) underwent surgery. Anesthesia and the basic surgical technique have been described elsewhere. 29 A pediatric cranial perforator and craniotome were used for preparation of two symmetrical, rectangular (15 × 18–mm) osteotomies in frontal bone (Fig. 1). The dura was detached from the bone with a spatula, and thermal damage was avoided using continuously flowing saline solution during bone preparation. The bone piece was repositioned without contact to the surrounding bone, and fixed on the right side with a four-hole titanium plate and miniscrews. On the left side, a PDLLA plate covering both the bone segment and the trephined holes (Fig. 1) and four SR-PLLA miniscrews (10 sheep) or four SR-PGA miniscrews (10 sheep) were used for fixation. Heat-shaping of the resorbable plate was unnecessary because of the flatness of the calvaria and pliability of the plate. After fixation, minimal inward movement of the bone segment on the resorbable side could be brought about by firm finger compression, but because of the flexibility of the plate, it immediately returned to its original position. The periosteum was sutured in the midline with No. 3-0 sutures and the wound was closed in layers. Flunixin (2.2 mg/kg) was administered before the animals awoke. Subcutaneously injected benzylpenicillin procaine (35,000 IU/kg) and intravenously administered phenylbutazone (8 mg/kg) were given postoperatively once a day for 3 days.

Analysis of Specimens

The animals were grouped according to the type of biodegradable screws used and electrically stunned before being killed at 4 (two PGA), 6, 12, 26 (two PGA and two PLLA at each interval), 52 (one PGA, one PLLA), and 104 weeks (one PGA, one PLLA). One sheep (PLLA group) was kept alive for the 3-year follow-up review. The heads containing SR-PGA screws and the heads of the sheep with SR-PLLA screws killed at 2-year follow-up were investigated using magnetic resonance (MR) imaging and plain x-ray films, because PGA implants in particular are associated with osteolytic and foreign body reactions. The MR studies were performed using a 0.1-tesla resistive unit and a head coil. A scout image obtained in a coronal direction was used to locate the craniotomy areas. The regions of the craniotomies were imaged in contiguous oblique slices. The examination included a T1-weighted pulse sequence (PS3D 125/20) with a flip angle of 80° and a T2-weighted pulse sequence (PS 110/40) with a flip angle of 90°. The image acquisition time was 2 and 24 seconds for the T1- and T2-weighted images. The slice thicknesses were 3 and 5 mm, respectively, and the matrix was 144 × 256.

Before plain x-ray films were obtained, the craniotomized areas were dissected free of soft tissue and removed with an oscillating saw. The bone specimens were examined in anteroposterior (AP) and tangential directions. The exposure settings were 48 kV, 25 to 32 mA and 42 to 44 kV, 25 mA with a film-focus distance of 100 cm. The AP images were analyzed as follows: the trephination holes were measured in two perpendicular directions, and the result was expressed as the mean diameter of the four holes. The length of the visible osteotomy line was measured and expressed as a percentage of the original line. All measurements were performed with the aid of a magnifying lens (× 7, with a precision scale of 0.1 mm).

The specimens were fixed in a graded series of ethanol immersions (70–99%) and embedded in methylmethacrylate. Five-micrometer-thick sections were cut from the center of the specimen through the screw line (sagittal plane) and stained by the Masson–Goldner trichrome method. Birefringent polymeric material in the specimen was identified in polarizing light.

Histomorphometric examination was used to analyze the effect of the fixation method and material on the consolidation process and formation of new bone (osteoid). 34 The nonconsolidated bone defect area was measured in windows corresponding to the original bone defect (original width 2.35 mm, window width 2.39 mm), using × 16 magnification (Fig. 2). The percentage of the remaining defect was expressed as the mean value of the plate and dural sides separately. Osteoid formation was analyzed in detail by using × 100 magnification in 10 standardized windows (0.37 × 0.61 mm, Fig. 2). Production of osteoid, which was laid on bony trabeculae, was measured by counting the length of the osteoid-covered surface and comparing it with the total trabecular bone surface. The areas of interest were the consolidating bone defect (four fields; the more poorly consolidated line was selected), the plate/periosteal and dural sides of the fixed bone segment (two fields each, measurements in intact dural area) and the control area (two fields). The control area was selected in the same specimen, in intact bone in the same sagittal plane (Fig. 2) in which the periosteum had been elevated. The presence of inflammatory cells within the sample fields was assessed qualitatively by using × 400 magnification for cell identification.

Statistical Analysis

All 4- to 52-week specimens were included in the statistical analysis. Differences in consolidation of craniotomy lines, osteoid surface fraction, and thickness of the fixed bone segment between resorbable and titanium fixation, between plate and dural sides, and between craniotomy line and control, and the effect of follow-up time were evaluated by repeated-measures analyses of variance. In these analyses, the fixations with the two types of resorbable miniscrews were analyzed separately.

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Sources of Supplies and Equipment

The 96/4 PDLLA plates and the Bionx SR-PLLA and SR-PGA miniscrews were manufactured at Tampere University of Technology, Tampere, Finland. The titanium miniplates and self-tapping titanium miniscrews were obtained from OsteoFix, Inc., Oulu, Finland. The 6/9 mm Heifetz pediatric skull trephine (model GB 340) and the Freiburg pattern pediatric craniotome (model GB 292) were purchased from Aesculap, Tuttlingen, Germany. The Dexon 3-0 sutures were acquired from Sherwood Davis and Geck, Gosport, England. The flunixin (Finadyne 50 mg/ml) was purchased from Orion, Espoo, Finland; the benzylpenicillin procaine (Ethacilin vet injekt 300,000 IU/ml) from Intervet, Boxmeer, Holland; and the phenylbutazone (Reumuzol vet injekt 200 mg/ml) from Lääkefarinjekt 300,000 IU/ml) from Intervet, Boxmeer, Holland. The MR imager (Merit model) was acquired from Picker Nordstar Co., Helsinki, Finland.

Results

All lambs recovered uneventfully. No neurological symptoms, infections, or clinical foreign body reactions were seen. During dissection, the osteotomies were stable on palpation, and the investigations showed no loss of fixation or even minimal dislocation of the bone segment in any animal. Titanium plates and screws had translocated passively into the bone tissue and frontal sinus at 52 to 104 weeks. The SR-PGA screws had disappeared at 6 weeks. The SR-PLLA screws were still palpable at 52 weeks but had disappeared at 104 weeks.

Four- to 12-Week Specimens

On plain x-ray films (AP views), approximately 7.3% of the craniotomy lines appeared to be consolidated on the SR-PGA side and 9.3% on the titanium side at 4 weeks, and 28% and 60.7% at 12 weeks (SR-PGA and titanium sides, respectively; Fig. 3). In cross sections obtained for histological examination (Fig. 2), the craniotomy lines were filled with dense connective tissue that was slowly replaced with irregular bone growth from the bone margins. In those cross sections, 38.3% of the original bone defect was left in the SR-PGA group and 25.9% in the titanium group at 4 weeks. At 6 weeks, the defects were still 34.8% and 24.6%, respectively, and 26.2% in the SR-PLLA group. At 12 weeks, the defects had diminished to 18.3%, 9.2%, and 14.9% (SR-PGA, titanium, and SR-PLLA, respectively). The originally straight craniotomy lines became diagonal, especially on the resorbable fixation side, and the defects were connected to a hole existing in the resorbable plate in nine of 13 oblique lines (five SR-PLLA, four SR-PGA) observed in the 6- to 12-week specimens.

The PDLLA plate was encapsulated in connective tissue, which was thickest at 4 to 6 weeks and thereafter slowly thinned and matured. At 4 to 6 weeks a few giant cells, macrophages, and lymphocytes were found on the implant surface. At 12 weeks bone growth on the plate was observed, and inactive giant cells lined the bone-covered plate. The connective tissue capsule was very thin around the titanium implants and the foreign body reaction was minimal. A few giant cells, macrophages, and lymphocytes were found around titanium implants, and the amounts diminished between 4 and 52 weeks.

Specimens Obtained at 26 to 52 Weeks

At 26 weeks, consolidation identified on radiographic studies (Fig. 3) had proceeded to 31.8% (SR-PGA) and 33.7% (titanium) of the entire craniotomy line, and at 52 weeks it was 91.1% and 85.7%, respectively. On histological examination, narrow lines through the bone were seen in 13 of 28 lines assessed at 26 to 52 weeks, eight on resorbable (five SR-PLLA and three SR-PGA) and five on the titanium sides (Fig. 4). Between 26 and 52 weeks, the osseous defects diminished from 35.4 to 0% in the SR-PGA group, from 19.9 to 8.9% in titanium-fixed osteotomies, and from 15.1 to 9.9% in the SR-PLLA group. The consolidation pattern varied between the follow-up groups, especially at 26 weeks in the group that underwent SR-PGA fixation. These two sheep had iatrogenically induced dural defects, with a piece of dura attached to the osteotomized bone segments (Fig. 5). The lesions had healed incompletely and had led to local 3- to 7-mm-wide and 1- to 5-mm-high herniations of the brain tissue and resorption of bone over the lesion. However, the outer.
bone surface was smooth on both sides, and no signs of fistulas or cerebrospinal fluid leakage were seen. In these particular animals, the unconsolidated craniotomy lines were large (23.8–47%, Fig. 6) and there was reduced osteoid formation in the craniotomy lines (Fig. 7).

The PDLLA plate had become wavy and was surrounded by a 0.5-mm-thick fluid layer, which contained active giant cells, macrophages, lymphocytes, and plasma cells. Macrophages and giant cells were seen penetrating the cracks of the plate. The edges of the device were covered by a thin bone layer, and in these protected areas, the capsule around the plate was thin and inactive. At 52 weeks, the plate had become fragmented and hydrolyzed, and the polymeric debris was encapsulated in mature, densely vascularized connective tissue and was undergoing absorption by foamy macrophages and giant cells (Fig. 8 upper). The bone surface was irregular and lacking osteoid under the resorptive areas, and osteoclasts were occasionally found.

Specimens Obtained at 104 Weeks

On radiological studies it was demonstrated that 93% of the osteotomy lines had consolidated (Fig. 3). Results of histological studies showed incomplete consolidation in two of eight lines, one in the SR-PGA group (4.8%) and one in the titanium group (estimated at 10–15%).

The entire PDLLA plate had disappeared at 104 weeks. The bone surface was smooth and covered with dense lamellar connective tissue, which was abundantly vascularized adjacent to the bone surface. In the specimen with
was noted for all types of fixation (Fig. 7). Osteoid formation was most active in areas adjacent to the dura, with a 68 to 100% osteoid-producing trabecular bone surface (Fig. 9). In the middle of the consolidating osteotomy lines (Fig. 7), osteoid formation was less active (32–80%), and on plate and periosteum sides (Fig. 9) it was as low as 20 to 58%. In areas with dural lesions (SR-PGA fixation group at 26 weeks), osteoid formation was minimal (10–23%) when compared with adjacent intact dura, above which the osteoid surface fraction was 68 to 82%. In addition, there was reduced osteoid formation in the craniotomy lines (Fig. 7). In the long term, total osteoid production was higher on sides treated with resorbable materials than titanium-treated sides, in which local bone growth was restricted (Fig. 9).

Consistent and high osteoid formation appeared to result in increased thickness of the osteotomized bone segment (Fig. 10). On the side treated with resorbable materials, bone was an average of 0.5 mm thicker than on the titanium-treated side, and the difference was significant in the SR-PGA fixation group (p < 0.01). No significant difference in thickness was observed between the groups treated with resorbable fixation materials.

Discussion

Chemistry of the Biomaterial

Biodegradable PLA and PGA are produced by polymerization of lactide or glycolide. Degradation occurs mainly by hydrolysis, and the resultant lactic acid and glycolic acid molecules are metabolized into carbon dioxide and water and eliminated by respiration. Hydrophobic PLLA has the slowest rate of degradation, which can be accelerated by combining the two isomeric forms, L- and D-lactic acids. Hydrophilic PGA degrades fastest, and the copolymer PLA–PGA has a degradation velocity that...
depends on the PLA–PGA polymeric ratio. Clinically, even more important than degradation velocity is the fact that the strength of a polyester implant declines before macroscopically observable degradation begins.

Clinical Significance

No complications caused by resorbable osteosynthesis devices were observed during the 104-week follow-up period, and there were no clinically significant differences in healing between the osteotomies fixed with resorbable or metallic materials. The resorbable fixation system, especially with rapidly degrading SR-PGA miniscrews, allowed unrestricted local bone growth and skull expansion. Local bone growth definitely was restricted on the titanium side, which has been proven in several studies. In addition, the bone segments transiently fixed with SR-PGA miniscrews remained thicker than titanium-fixed segments, which has also been demonstrated earlier. As in previous reports, passive translocation of the metallic implants into the bone and frontal sinus were observed. Translocated devices may lead to a potential risk of infection and brain damage and may complicate later surgery.

Delayed Consolidation

Despite the rapid period of growth of the animals, bone consolidation was uneven and incomplete in both the resorbable and metallic fixation groups. During the first 4 weeks, 60 to 70% of the original bone defect had consolidated from the bone margins. Thereafter, consolidation slowed remarkably against the vertically oriented connective tissue filling the bone defect. Prevot, et al., reported a lack of ossification after cranioplasty in 6.3% of children younger than 1 year old and in 2.8% of children older than 18 months. Our hypothesis was that ossification could be enhanced by a protective resorbable plate with a “ceiling effect” according to the principle of guided bone regeneration. However, connective tissue invasion was rapid and occurred freely through the holes in the plate. In our previous study, guided bone regeneration along punched SR-PLLA plates was shown in craniotomy lines in slowly growing sheep with thicker skulls. In the present study, the osteogenic importance of the dura was emphasized in animals with dural lesions, which is in line with earlier experimental and clinical reports.

Biocompatibility of the Resorbable Materials

Delayed transient sterile inflammatory reactions are particularly associated with large PGA implants used for malleolar fracture fixation. The incidence of late inflammatory reactions to PLLA has also been high, when 2-mm-thick high-molecular-weight PLLA plates have been used for fixation of zygomatic fractures with minimal soft-tissue coverage. The screws used in the present study were tiny, and the plate was 0.4 mm thick. In this study, no...
clinical foreign body reactions were observed, absorption of the PDLLA plate was complete, and the bone surface was smooth and dense at 2 years.

**Possible Clinical Applications**

The SR technique enables metallike initial mechanical properties in biodegradable materials and manufacture of strong miniimplants. Reinforced, slowly degrading plates and screws are suitable for fixing osteotomies in loaded conditions in slowly growing individuals, and wide, occluding plates may be used for covering bone defects. Reinforced, delicate plates and miniscrews with faster resorption qualities could be used in nonloaded conditions in infants. If large plates are used to cover bone defects in children, restriction of skull growth could be prevented by using rapidly resorbable screws. The radio-lucency of these biodegradable osteosynthesis devices facilitates both postoperative follow-up studies and radiation therapy after tumor surgery.

**Conclusions**

Rigid metallic fixation devices cannot secure complete osseous consolidation in even minor osseous defects in growing calvarial bone and can be substituted by a semirigid, thin biodegradable plate and miniscrews. These facts, together with the passive translocation of metallic implants and local growth alterations, emphasize the importance of developing an optimal resorbable miniosteosynthesis system for children.

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**Disclosure**

None of the authors except Professor Törmällä has a financial interest in the Bionx miniscrews, and the plates used in this study were research samples.

**References**

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Address reprint requests to: Timo Waris, M.D., Ph.D., Department of Plastic Surgery, Oulu University Central Hospital, PL 22, 90221 Oulu, Finland. email: twaris@sun3.oulu.fi.