FOREIGN-BODY REACTION AND THE COURSE OF OSTEOLYSIS AFTER POLYGLYCOLIDE IMPLANTS FOR FRACTURE FIXATION
EXPERIMENTAL STUDY IN SHEEP

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Foreign-body reaction to polyglycolide (PGA) implants has been described in man. Many animal experiments have verified the mechanical properties of fixation devices made from PGA, but a significant foreign-body reaction has not been described. We studied the effect of PGA rods in 12 sheep with standardized osteochondral fractures of the medial femoral condyle fixed with uncoloured, self-reinforced PGA rods (Biofix).

Radiographs were taken at intervals ranging from two weeks to two years, and the sheep were killed at intervals ranging from six to 24 months. All knees were examined histologically.

Eleven of the 12 fractures healed radiologically and histologically. Moderate to severe osteolysis was seen at four to six weeks with maximum changes at 12 weeks in ten animals. Six knees showed fistula-like connections between the implant site and the joint space. Three developed synovitis, one with inflammatory changes involving the whole cartilage and one with destruction of the medial condyle.

Although in our study osteochondral fractures fixed with PGA rods healed reliably, there were frequent, significant foreign-body reactions. Caution is needed when considering the use of PGA fixation devices in vulnerable regions such as the knee.

Received 27 July 1995; Accepted after revision 17 October 1995

The biocompatibility of biodegradable synthetic polymers used as suture materials has been described in many studies (Kulkarni et al 1966; Herrmann, Kelly and Higgins 1970; Katz and Turner 1970; Frazza and Schmitt 1971; Conn et al 1974; Ray et al 1981). In 1985, their good mechanical properties led to the introduction of implants made of polyglycolide (PGA) for the fixation of fractures (Rokkanen et al 1985; Böstman et al 1987; Rehm, Helling and Claes 1989; Hoffmann et al 1989; Leixnering, Moser and Poigenförst 1989; Ruf, Schult and Buhl 1990). The process of degradation and the tissue response have been described by many authors (Hollinger and Battistone 1986; Vainionpää 1986; Vainionpää et al 1987; Laiho, Mikkonen and Törnäälä 1988; Pellinen et al 1988). PGA and other biodegradable poly-α-hydroxyacids such as polylactide (PLA) or polydioxanone (PDS) cause a mild, non-specific inflammatory response with invasion of macrophages, multinucleated foreign-body giant cells and neutrophilic polymorphonuclear leucocytes (Brady et al 1973; Reed and Gilding 1981; Vert and Chabot 1981; Rehm and Schultheis 1985; Bos et al 1991).

Soon after these implants began to be used in man, Böstman et al (1987) reported formation of a sterile sinus after internal fixation of ankle fractures with PGA rods. Since then other reports have shown that these foreign-body reactions occur in varying degrees of severity ranging from osteolytic changes to intense granulomatous inflammatory soft-tissue lesions (Poigenförst, Leixnering and Ben Mokhtar 1990; Böstman 1991, 1992). The incidence depended on the anatomical location and ranged from 4% to 14.6% in ankle fractures to 22.5% to 40% in wrist fractures (Table I) (Hirvensalo 1989; Casteleyn, Handelberg and Haentjes 1992; Frokjaer and Moller 1992; Hoffmann et al 1992).

Animal experiments have verified the mechanical properties and biocompatibility of fixation devices made from PGA (Mäkelä et al 1988; Axelsson 1989; Böstman et al 1992b,c; Päivärinta et al 1993), but no assessment of foreign-body reactions has been described nor has there been a study of the long-term fate of PGA implanted in bone.

We have examined the incidence, intensity and the course of foreign-body reactions during the degradation of uncoloured, self-reinforced PGA rods in an animal model.
MATERIALS AND METHODS

We used 12 female Merino sheep weighing 38 to 57 kg (mean 44.25). After sedation with intramuscular xylazine they were anaesthetised with intravenous sodium thiopental and intubated. General anaesthesia was maintained with halothane and nitrous oxide for the duration of the operation. The left hind leg was prepared in a standard sterile fashion. The medial femoral condyle was exposed through a lateral arthrotomy without release of the medial collateral ligament. A 15 mm osteotome was used to create an unstable horizontal osteochondral fracture in the main weight-bearing area, as described by Claes et al (1986). The fragment was removed, measured and then anatomically reduced. The average length was 17.8 mm (15 to 21) and the average width 16.5 mm (13 to 25).

The fractures were stabilised using three 2 mm uncoloured self-reinforced PGA rods (Biofix; Bioscience Ltd, Tampere, Finland) of mean length 22.4 mm (15 to 25), inserted through 2 mm holes previously drilled in divergent directions.

The medial capsule was closed with biodegradable PGA sutures over an intra-articular suction drain. The wound was closed in two layers and radiographs in two planes were obtained. The sheep were returned to their cages and were immediately able to bear full weight on the left leg without external immobilisation. Postoperative analgesia consisted of 50 mg tramadol and 1 g metamizole intra-muscularly for three days after operation.

All sheep were reviewed radiographically and the first five were killed after six months. Two of the remaining sheep were killed after one year, two after 18 months and one after two years. The knees were excised and inspected. Radiographs were obtained in two planes and histological examination undertaken. The last three sheep had CT of the knee.

Specimens were fixed in buffered formalin, dehydrated in ethanol and embedded undecalcified in methylmethacrylate (Boellaard and von Hirsch 1959; Schenk 1965). Transverse (proximal) and sagittal (distal) sections, 15 μm and 50 μm thick, were cut with a microtome and stained with paragon for fluorescence microscopy. The synovial membrane and the appropriate inguinal lymph nodes were biopsied and stained with haematoxylin and eosin. We performed polychrome sequential labelling on five sheep according to the technique described by Rahn and Perren (1971) and Rahn (1976). Calcein green (10 mg/kg subcutaneously) was given two weeks after operation, xylencol orange (90 mg/kg subcutaneously) after four weeks and pyrrolidino-methyltetracycline (25 mg/kg intravenously) three days before the knees were removed. A single tetracycline marking was performed on two sheep six and 12 months before death. For fluorescence microscopy a Leitz Ploemopak 2.4 system (Leitz Wetzlar GmbH, Germany) was used. Light microscopy was used to assess both fracture healing and inflammatory changes and polymer particles were identified under polarised light.

**Table I.** Review of the literature on foreign-body reaction in man to fracture fixation devices made of PGA

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Location</th>
<th>Sterile sinus formation (%) (appearance after operation in weeks)</th>
<th>Osteolytic changes (%) (appearance after operation in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Böstman et al (1987)</td>
<td>28</td>
<td>Ankle</td>
<td>7.1 (12 to 16)</td>
<td></td>
</tr>
<tr>
<td>Böstman et al (1989)</td>
<td>102</td>
<td>Ankle</td>
<td>5.9 (8 to 12)</td>
<td></td>
</tr>
<tr>
<td>Hirvensalo (1989)</td>
<td>41</td>
<td>Ankle</td>
<td>14.6 (12)</td>
<td></td>
</tr>
<tr>
<td>Böstman et al (1990)</td>
<td>516</td>
<td>Variety</td>
<td>7.9 (7 to 16)</td>
<td></td>
</tr>
<tr>
<td>Hirvensalo, Böstman and Rokkanen (1990)</td>
<td>24</td>
<td>Radial head</td>
<td>8.3 (8 to 12)</td>
<td></td>
</tr>
<tr>
<td>Böstman (1991)</td>
<td>67</td>
<td>Ankle</td>
<td></td>
<td>50.7 (6 to 52)</td>
</tr>
<tr>
<td>Frokjaer and Moller (1992)</td>
<td>25</td>
<td>Ankle</td>
<td>4.0 (8)</td>
<td>36.0</td>
</tr>
<tr>
<td>Böstman (1992)</td>
<td>286</td>
<td>Ankle</td>
<td>6.3 (1)</td>
<td></td>
</tr>
<tr>
<td>Böstman et al (1992d)</td>
<td>216</td>
<td>Ankle</td>
<td>11.1 (5 to 26)</td>
<td></td>
</tr>
<tr>
<td>Hoffmann et al (1992)</td>
<td>40</td>
<td>Distal radius</td>
<td>22.5 (4 to 16)</td>
<td></td>
</tr>
<tr>
<td>Casteley et al (1992)</td>
<td>15</td>
<td>Distal radius</td>
<td>40.0 (8 to 18)</td>
<td>60.0 (12 to 24)</td>
</tr>
<tr>
<td>Gerbert (1992)</td>
<td>23</td>
<td>Foot</td>
<td>4.3 (12)</td>
<td>30.4 (6 to 12)</td>
</tr>
<tr>
<td>Fraser and Cole (1992)</td>
<td>21</td>
<td>Variety in children</td>
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<td>14.3 (12)</td>
</tr>
<tr>
<td>Lob et al (1993)</td>
<td>42</td>
<td>Variety</td>
<td>4.8</td>
<td></td>
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<tr>
<td>Ahl et al (1994)</td>
<td>32</td>
<td>Ankle</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Stötzer and Ruf (1994)</td>
<td>35</td>
<td>Ankle</td>
<td>14.3 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Svensson et al (1994)</td>
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<td>Variety</td>
<td>4.0 (8)</td>
<td></td>
</tr>
<tr>
<td>Ruf, Stötzer and Schult (1994)</td>
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<td>Ankle</td>
<td>5.0 (8 to 12)</td>
<td></td>
</tr>
<tr>
<td>Lavery et al (1994)</td>
<td>9</td>
<td>Foot</td>
<td>0.0</td>
<td>55.6</td>
</tr>
</tbody>
</table>
RESULTS

Primary wound healing was achieved in all the animals and there were no postoperative complications. All the sheep limped for three to seven days after the operation and then moved normally. They were transferred to a shepherd four weeks after operation, but two vanished unaccountably after six months due to causes unrelated to this study. We included their radiographs, however, in the evaluation.

When the knees were removed eight out of ten showed smooth joint surfaces. In six, there were fistula-like connections of varying severity at the sites of drilling and in two of them also in the tibial plateau. These small cylindrical cavities were continuous with the knee. After six months three sheep showed thickening and a villous appearance of the synovial membrane. One knee had inflammatory destruction of the medial condyle (Fig. 1) and one showed inflammatory changes involving the entire cartilage area with cystic changes on the chondral surface and ingrowth of synovial membrane. No bacteria were grown from these knees. Specimens removed later appeared normal.

Bony union was found in 11 of the 12 knees. The one displacement occurred after four weeks and the postoperative radiograph showed insufficient fixation of the osteochondral fracture, and later, moderate osteolytic changes at the rod site. All specimens with polychromic sequential labelling showed intense fluorescence at the fracture site and within the osteochondral fragment, indicating undisturbed fracture healing and good nutrition of the fragment.

Table II. Occurrence of osteolysis* at the rod site after operation as seen on plain radiographs

<table>
<thead>
<tr>
<th>Sheep</th>
<th>Weeks</th>
<th>Months</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
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<tr>
<td>8</td>
<td>+</td>
<td>+</td>
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<tr>
<td>11</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

*0 = no osteolytic changes visible; + = mild osteolysis (osteolytic changes at the rod site); ++ = moderate osteolysis (cystically extended osteolysis); +++ = severe osteolysis (confluence of osteolyses)

After four weeks radiographs showed osteolytic changes at the rod site which was classified as mild to severe (Table II). In ten knees moderate to severe osteolysis was seen at between two and six weeks on plain radiographs (Fig. 2) with maximum changes at 12 weeks (Table II). The widest of these radiolucencies was usually found in the distal part of the implant site. Radiographs showed regression of the osteolytic foci in only two knees, and all had an increasingly densely mineralised trabecular rim (Fig. 3a).
After six months histological examination showed a first new bony formation at the margin of the osteolysis. The development of an increasingly dense trabecular rim was later seen histologically, as observed on the radiographs. Slow and isolated new bone formation could be seen developing within the osteolysis after six months; this was confirmed by late tetracycline marking (Fig. 4). After 18 months only one specimen showed almost complete restitution of the implant site, and here the osteolytic changes had been mild (Fig. 5). The knee removed at 24 months still had evidence of moderate osteolysis with only a trace of new trabecular bone (Fig. 3b).

In all sheep killed after six months histological examination under polarised light still showed polymer particles surrounded by a dense infiltration of granulocytes and macrophages. Migration of this debris to the medullary cavity and into the fistula-like former sites of drilling was seen after six months in two knees (Fig. 6). In all specimens there were intracellular polymer particles in macrophages within the associated inguinal lymph nodes at between six and 24 months (Fig. 7). Histological examination of the nodes showed them to be reactive with proliferation of secondary follicles and extended sinuses, but these changes regressed after 12 months. After six months, synovial
biopsy showed synovitis with ulcerative lesions or dense invasion of mononuclear round cells in two knees and only fibrous scar tissue in three. Later specimens showed non-specific proliferation of the superficial synovial cells. Polymer particles were not seen at the synovial surface.

DISCUSSION

PGA rods are a reliable device for the fixation of osteochondral fractures. The excellent results published by Greve and Holste (1985), Claes et al (1986) and Plaga et al (1992), using PDS rods with inferior mechanical properties and no postoperative immobilisation, support this view. The initial enthusiasm for biodegradable implants in fracture fixation was tempered by early reports of foreign-body reactions.

The occurrence and a potential cause of such problems differ according to the polymer involved. Research and discussion should therefore be strictly individualised for the different polymers such as PGA, PDS and PLA and their copolymers and stereocopolymers.

The osteolytic changes first described by Böstman (1991) should be viewed as the expected reaction to the PGA implant and not as a complication. The incidence of these changes varied from 14.3% to 60% in patients (Table I) and was as high as 100% in our animal experiments (Casteleyn et al 1992; Fraser and Cole 1992; Frokjaer and Moller 1992; Gerbert 1992). Mild osteolytic changes at the rod site probably have no effect on fracture healing or on the static properties of the bone. If these changes exceed a certain level, however, they are likely to interfere with fracture healing especially in apical fractures, particularly since their first occurrence four to eight weeks after surgery is within the period of fracture healing. Svensson, Janarv and Hirsch (1994) reported two cases of severely impaired healing of fractures of the radial head with sequestration, resulting in the subsequent removal of the radial head. In the one case of fracture displacement in our study it is not clear whether this was due to inadequate fixation or the intensive osteolytic changes. Although total regression of the osteolytic changes is likely it should not be expected within the first two years after implantation.

The initial view that the foreign-body reaction was solely due to the pigmentation of the PGA rods was discredited when it was also observed after the use of uncoloured material. Santavirta et al (1990) reported the same immunological response to coloured and uncoloured PGA rods. Böstman et al (1992d), however, found that the incidence of sterile sinus formation decreased from 18.1% to 4.5% after the use of uncoloured PGA screws in ankle fractures. They also suggested that the increasing number of fragments of

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**Fig. 5**

After 18 months of implantation, there are no polymer remnants and complete bony restitution of a proximal rod site (R) (transverse cut, polarised light X 1.8).

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**Fig. 6a**

After six months of implantation, there is polymer debris within the osteolysis (O) and the connective tissue of the former drill-hole with a connection to the joint space (arrow) (sagittal cut, polarised light X1.5).

**Fig. 6b**

After six months of implantation, there are polymer rod remnants within the osteolysis (O) and migration of polymer debris to the medullary cavity (arrow) (transverse cut, polarised light X1.5).
low molecular weight led to an increased osmotic pressure within the implant site (Böstman et al 1992a). Formation of a sinus could be prevented if the debris was expelled into the medullary cavity and might therefore be dependent on the density of bone trabeculae. This may explain the variable incidence of sterile sinus formation in different anatomical locations. It also appears clear that the close proximity of the implant site to the medullary cavity leads to a reduced amount of polymer particles in this region which may also explain why the maximum degree of osteolysis is typically seen in the distal zone of the implant site (Fig. 2). Polymer debris may also be extruded through the connective tissue within the fistula-like changed former drill-hole (Fig. 6a).

Why do osteolytic changes occur during the degradation of some biodegradable polymers? The debris of non-degradable polymers such as polyethylene or polymethylmethacrylate used in total joint replacement produces bone resorption by macrophage activation (Murray and Rushton 1990; Horowitz et al 1991; Langkamer et al 1992). This leads to the release of mediators including prostaglandins or interleukins with the subsequent activation of osteoclasts and bone resorption (Klein and Raisz 1970; Cohn 1978; Minkin and Shapiro 1986; Ishimi et al 1990). An accumulation of macrophages at the tissue implant interface was also described during the degradation of PGA screws by Päivärinta et al (1993) with the maximum amount seen 12 weeks after operation at the same time as the maximum degree of osteolysis (Tables I and II). It is reasonable to assume that there is a correlation between macrophage activation and the appearance of osteolytic changes, although Päivärinta et al (1993) reported no such change.

During the degradation of biodegradable materials fragments of varying size are released from the implant and are phagocytosed primarily by macrophages (Tabata and Ikada 1988; Rozema et al 1992). With poly(L-lactic acid) Lam et al (1992b) were able to show that macrophages and granulocytes phagocyte the polymer debris leading possibly to death of the macrophages with a consecutive inflammatory response. Cell death appeared to depend on the amount of phagocytosed particles regardless of whether one large fragment or several smaller ones were incorporated. This supports the suggestion that a slow rate of degradation may increase the biocompatibility by a reduction in the amount of polymer fragments released per unit time. Why do other biodegradable materials with a comparable degradation rate, such as PDS, show less foreign-body reaction? Five different follow-up studies showed no osteolytic changes or inflammatory tissue reactions during the degradation of PDS rods after fixation of first metatarsal osteotomies or toe arthrodeses in 171 patients (Patton, Shaffer and Kostakos 1990; Brunetti, Trepal and Jules 1991; Gerbert 1992; Bashara et al 1994; Laverty et al 1994).

Different PLA polymers show osteolytic changes with a lower incidence and intensity, although PLA has a significantly protracted degradation rate compared with PGA (Helling et al 1994; Suuronen et al 1994). A slower rate of degradation is of primary importance regarding the biocompatibility of a biodegradable implant, especially with regard to soft-tissue reactions. Even sterile sinus formation may be provoked by PLA implants if the implant volume exceeds a certain level. Eitenmüller et al (1989) reported sterile sinus formation after internal fixation of ankle fractures with large PLLA plates and screws.

Other factors appear to contribute to biocompatibility. Matlaga, Yasenchak and Salthouse (1976) and Lam et al (1992a), using degradable and non-degradable polymers, showed that even the shape of the implant affects the intensity of an inflammatory response, but it is uncertain whether this may be due to the rapidly exposed inner fibre structure of the self-reinforcement of the PGA rod, and this is still under discussion. Furthermore, the crystallinity of a biodegradable implant, which prevents late hydrolytic degradation of polymer debris, may result in a foreign-body reaction (Lam et al 1992b; Rozema et al 1992; Bergsma et al 1993).

In all the knees which we studied after six months there were still crystalline particles within the areas of osteolysis, surrounded by a large number of granulocytes and macrophages. This has also been found within the discharge after sterile sinus formation in ankle fractures (Böstman et al 1992d). Although PGA rods are expected to be degraded by this time, we found crystalline remnants in macrophages from the appropriate inguinal lymph nodes. Even at 24 months after surgery we found polymer debris in the lymph nodes although there was no more at the implant site. This appearance was first described by Verheyen et al in 1993 for poly(L-lactide).

Daniels et al (1992) and Taylor et al (1994) suggested that the local decrease in pH at the implant site during the degradation is one of the main reasons for the inflammatory tissue response and further data are now available on biocompatibility from investigations in vitro on the toxicity of
acid monomers which are released during the degradation of poly-α-hydroxyacids. Ignatius and Claes (1996) have shown that the accumulation of poly(L/DL-lactide) and poly(L-lactide-co-glycolide) degradation products may reduce growth in cell culture. The toxic influence depends on a high concentration of degradation products after pH adjustment. This may explain why even amorphous and slowly degrading polymers may produce osteolytic changes if there is not sufficient drainage of by-products into the surrounding tissue.

As soon as there is a connection between the implant site and the joint space the synovial membrane comes into contact with the polymer debris. Barfod and Svendsen (1992) and Friden and Rydholm (1992) reported cases of severe synovitis after the intra-articular use of PGA rods and polymer debris, surrounded by foreign-body giant cells, was identified as the cause. In our study three of the five sheep with a fistula-like connection between the implant site and the joint space showed inflammatory changes in the synovial membrane after six months, although we did not see the typical histological findings described by Barfod and Svendsen (1992). This could possibly be explained by the fact that the acute arthritis described in the literature between six and 12 weeks after surgery would have settled before our biopsies were taken at six months.

We consider that clinicians should proceed with caution when considering the use of PGA fixation devices particularly in vulnerable regions such as the knee. Biodegradable internal fixation is still a promising alternative in the fixation of osteochondral fragments, apical fractures or paediatric fractures, but studies on biocompatibility should have a high priority: tissue reaction depends on a large variety of factors. Long-term studies in vivo are necessary, not only until the mechanical properties of the implant have been lost, but also until it is completely degraded with the disappearance of all traces of the material. All biodegradable fixation devices must be tested for their intraosseous and intra-articular biocompatibility before clinical use.

This study was partially sponsored by a grant of Biovision GmbH, Umkirch Germany and a grant of the Freundes und Förderer der Universität zu Köln. Although none of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, benefits have been or will be received but will be directed solely to a research fund, foundation, educational institution, or other non-profit organisation with which one or more of the authors are associated.

References


