

Enhancing Biocompatibility : Second Generation Biodegradable Implants



Publisher: Inion OY, Lääkärintätkä 2, FIN 33520, Tampere, Finland
T +358 3 230 6600
F +358 3 230 6601
W www.inion.com

Introduction

Biodegradable polymers are becoming more popular as implant materials in orthopaedics. The main advantage of biodegradable implants in contrast to metals is that they eliminate the need for a second surgical intervention for removal of the devices. However, they have not been universally adopted which may be due to the historically higher level of local foreign-body reaction than is typically observed with metal implants. (Böstman and Pihlajamäki 2000)

The process of biodegradation of a polymer implant begins with the polymer chains being broken into smaller fragments by hydrolysis (Fig.1). The molecular weight of the implant decreases first. Thereafter the mechanical strength of the implant decreases allowing subsequent mechanical fragmentation and absorption of the implant to begin. Actual mass loss of the implant occurs then through the release of soluble degradation products, phagocytosis by macrophages and histiocytes, intracellular degradation and finally, metabolic elimination through the citric acid (Krebs) cycle to carbon dioxide and water, which are expelled from the body via respiration and urine.

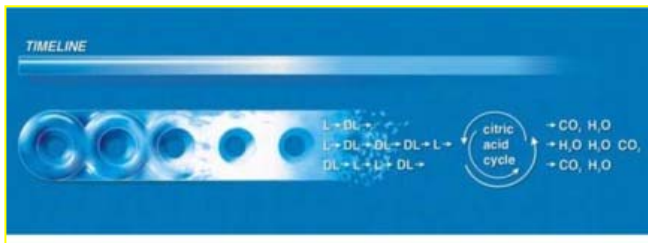


Fig 1. The biodegradation process

There is a danger of adverse tissue reaction if the rate of implant degradation produces more debris particles than the tissue is able to tolerate. This risk is greatest when the gross geometry of the implant is rapidly lost. (Böstman and Pihlajamäki 2000, Middleton and Tipton 2000)

In most cases, the symptoms of the tissue reaction are subclinical and pass unnoticed, but in some patients a clinically manifest inflammatory foreign-body reaction ensues. The clinical manifestation occurs in varying levels of severity from redness, mild fluid accumulation and discharging sinus formation to irreversible tissue damage. In adults these reactions appear to be independent of the age and gender of the patients. In many clinical studies the reported incidence of inflammatory reactions has been small and the reactions themselves mild enough to have no effect on the long-term outcome. (Ambrose and Clanton 2004,

Böstman and Pihlajamäki 2000) These reactions, if they occur, typically will manifest in the latter stages of implant degradation i.e. 6-12 months post operatively. In children, the tissue reactions appear to be quite rare (2.1 % of cases with polyglycolide implants) and always mild in character (Rokkanen et al. 2000, Athanasiou et al. 1996).

All implants cause tissue response but this varies radically

It is important not to confuse these tissue reactions with the normal physiological responses to any implantation or, indeed, surgery. All forms of implantation involve some degree of tissue injury which induces a physiological healing response. This consists of two essential components: inflammation and repair processes that represent a spectrum of interdependent molecular and cellular responses. In the case of an implant, its foreign nature tends to induce a chronic inflammatory response characterized by a granulomatous reaction. Acute inflammation can be superimposed and is especially marked if bacterial infection arises. (Kirkpatrick et al. 2002) The rate of bacterial infections is not related to the implant material, and it has been shown to be the same after implantation of metal and biodegradable materials. (Sinisaari 2004)

Adverse tissue response rates of up to 47% have been recorded with PGA

Adverse tissue responses to fixation implants made of polyglycolide have been reported in more than 15 clinical studies. The incidence has varied from 2.0 to 46.7 %. In studies concerned with polylactide implants, the adverse tissue reaction rate has usually been lower than with polyglycolide. In a recent study, a clinically significant foreign-body reaction occurred in one patient among 491 treated (0.2%). Another clinical study of polylactide implants reports fluid accumulation in 3 patients out of 1043 operated (0.3%). The timing of these adverse tissue reactions has been up to two years after surgery. The highest tissue reaction rates have been observed in bone sections with a recognizably poor vascularity. (Ambrose and Clanton 2004, Böstman and Pihlajamäki 2000)

It has been speculated that the higher level of reactions to polyglycolide based implants result from the hydrophilic nature of the material. This causes more rapid decomposition than the hydrophobic and slower degrading lactide-based implants. This in turn causes the rate of debris production to exceed the capacity of the tissue to process these breakdown products. (Böstman and Pihlajamäki 2000)

Although there is a significant body of literature on adverse tissue reactions to biodegradable polymer implants, a meaningful comparison of the complication rate between implants made of the same polymers but different manufacturers is made difficult by the fact that raw materials from different sources often differ considerably from each other in their characteristics. This, in turn, may affect the biocompatibility of the implants. (Böstman and Pihlajamäki 2000)

The Inion biodegradable implants are manufactured using the proprietary Inion OPTIMA™ family of materials made of polymer blends of polylactides, polyglycolides and trimethylene carbonate. This blending process has been developed in order to address the well-documented issues of biocompatibility. Inion selects the materials for each surgical application from this family to optimise product performance. There are currently four different product lines available:

- Inion CPS™ for cranio-maxillofacial fixation
- Inion OTPS™ for orthopaedic trauma fixation
- Sports medicine for meniscus and ACL/PCL repair fixation
- Dental for dental regenerative surgery

Methodology

This paper is a review of the tissue reactions that have been reported to Inion concerning products made using OPTIMA™ materials. The results gathered are from comments gathered in the course of the Customer Feedback Investigation rather than simple research reports.

There are limitations due to the nature of this method of data capture. Specifically these include the fact that data is not necessarily collected in a systematic fashion but in response to patient and customer comments. Moreover further investigation of comments is often not straightforward.

The data, therefore, is based on information that has been brought to the manufacturer's attention.

Inion CPS™ Biodegradable Fixation System

First introduced in May 2001 the Inion CPS™ Biodegradable Fixation System consists of plates, mesh plates and screws that are indicated for:

- Mandibular fixation (2.5 mm CPS™ System)
- Medium load-bearing midface and orthognathic fixation (2.0 mm CPS™ System)
- Low load-bearing cranial and midface fixation (1.5 mm CPS™ System)
- Paediatric craniofacial procedures (1.5 mm CPS™ Baby System)



Fig 2. Inion CPS Products in use

The total number of operations based on sales is estimated to be approximately 6000 during 2002-2004. Inion has received reports of adverse tissue responses in 0.3% (19) of patients and of infection in 0.05% (3) of patients. Twelve (12) of these cases are known to have occurred where there was limited soft tissue coverage over the implant site due to positioning of the implant. The reactions noted include:

- Swelling; from one month to a year after surgery
- Sterile abscess formation one year after surgery
- Fluid accumulation one year after surgery.
- Exfoliation of pieces of plate or screw six months after surgery.
- Granulation tissue from three to nine months after surgery.

The timing of the reactions ranged from 8 months to two years. Three of the reported cases resulted in plate removal. In all cases bone healing was uneventful.

Adverse tissue response rate 0.3% in Inion CPS products

Three patients were treated for suspected device-related infection by prescribing antibiotics. The symptoms occurred from two to six months after surgery.

In conclusion: the reported rate of Inion CPS™ Biodegradable Fixation System related adverse tissue responses is 0.3%. The reported rate of infection is 0.05%.

Inion OTPS™ Biodegradable Fixation System

The Inion OTPS™ Biodegradable Fixation System was introduced in June 2003 and comprises plates, mesh plates, screws and pins that are indicated for:

- Maintenance of alignment and fixation of bone fractures, osteotomies, arthrodeses or bone grafts (OTPS™ Pin)
- Maintenance of reduction and fixation of cancellous bone fractures, osteotomies or arthrodesis of the upper extremity, ankle and foot (OTPS™ Ankle)
- Bone graft & fragment containment, cement restriction in total joint arthroplasties, protective barrier for bone graft harvest sites (OTPS™ Mesh)
- Fixation of non-comminuted diaphyseal fractures of the metacarpal, proximal phalangeal middle phalangeal and osteotomies (OTPS™ Hand/Mini)

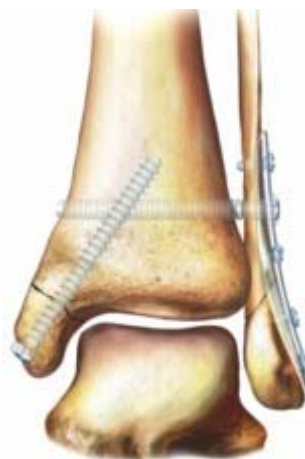


Fig 3. Inion OTPS Ankle Fixation System

The total number of operations during 2004 based on sales is estimated to be approximately 4200.

Table 1. The breakdown of the approximate number of operations performed by Inion OTPS™ product line products in the year 2004.

<u>Product</u>	<u>Number of operations in 2004</u>
Inion OTPS™ Ankle Fixation	630
Inion OTPS™ Malleolus and Syndesmosis Fixation	1,780
Inion OTPS™ Mesh	250
Inion OTPS™ Hand/Mini System	Limited amount
Inion OTPS™ Pin	1,540
TOTAL	4,200

Adverse tissue response rate less than 0.1% in Inion OTPS products

In conclusion, up to 2004, Inion had not received a single report of tissue reactions relating to the approved uses of the Inion OTPSP™ products.

Subsequently the data collected operations in selected countries as described in the Inion White Paper "Ankle Fractures" shows 3 infections (1,9 % from 160 patients group) and 1 adverse tissue reaction (0,6 % from 160 patients group).

Inion HEXALON™ and Inion TRINION™ – the Sports Medicine products

The Inion HEXALON™ and Inion TRINION™ Sports Medicine products are biodegradable fixation screws indicated for:

- Inion HEXALON™ : ACL/PCL repair
- Inion TRINION™ : Fixation of longitudinal vertical meniscus lesions located in the vascularized area of the meniscus



Fig 4. Inion HEXALON™



Fig 5. Inion TRINION™

HEXALON™ screws were introduced in May 2002 and since then it is estimated to have been used in 7000 operations, based on sales.

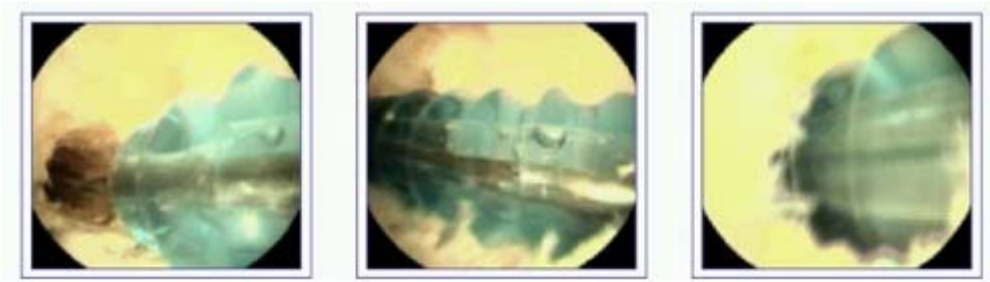


Fig 6. Inion HEXALON™ during arthroscopic insertion

TRINION™ was introduced in August 2004 and the total number of operations, based on sales, is estimated to be approximately 580.

There is a single report of swelling which occurred 6 weeks post-operatively and the screw was found to have broken in situ into 2-3 small pieces. A new operation was needed to remove the pieces.



Fig 8. Inion TRINION™ in situ

Adverse tissue response rate close to Zero for the Inion Sports Medicine Range

No infections have been reported in relation to these products. Inion has not received a single report on adverse tissue response relating to the use of the Inion TRINION™ meniscus screw.

Based on this single event we conclude an adverse tissue reaction rate of close to zero for the entire sports medicine product line.

Inion GTR™ Biodegradable Membrane System

The Inion GTR™ Biodegradable Membrane System for dental regenerative surgery was introduced in April 2004 and is indicated for:

- Surgical treatment of periodontal defects
- Pre-implant and peri-implant surgery
- Covering bone defects and empty sockets



Fig.9. Inion GTR Membrane in situ

The total number of operations performed with Inion GTR™ membrane is estimated to be 3160 based on sales. There is a single case report of a suspected infection relating to the use of the membrane. The patient developed swelling, pain and secretion of pus after an exposure of the

membrane. Symptoms were non-responsive to antibiotics and pain killers. The surgeon performed a second operation to remove the remnants of the membrane. After the procedure healing was normal and symptoms disappeared.

Based on these reports and the number of operations performed, there have been no reports of adverse tissue response rate to the Inion GTR™ membrane for on label use. We therefore assume that this rate and the rate of infection is close to zero.

Adverse response rate close to Zero in Inion GTR products

Conclusion

Prior to these implants being available the generally observed level of adverse tissue reactions and infections associated with polyglycolide biodegradable implants, observed in a variety of published material, was in the order of 2-46%. The level of adverse tissue reactions and infections associated with polylactide biodegradable implants has been observed at 0.2-0.3%.

Implants made using the blending techniques of Inion have been used in an estimated 21,000 procedures between 2002 and 2004. The manufacturer has received reports of 20 cases of adverse tissue reactions and 4 reports of infections relating to surgeries where these implants have been used.

The overall rate of adverse tissue responses is 0.1 % and infection rate is 0.02 %.

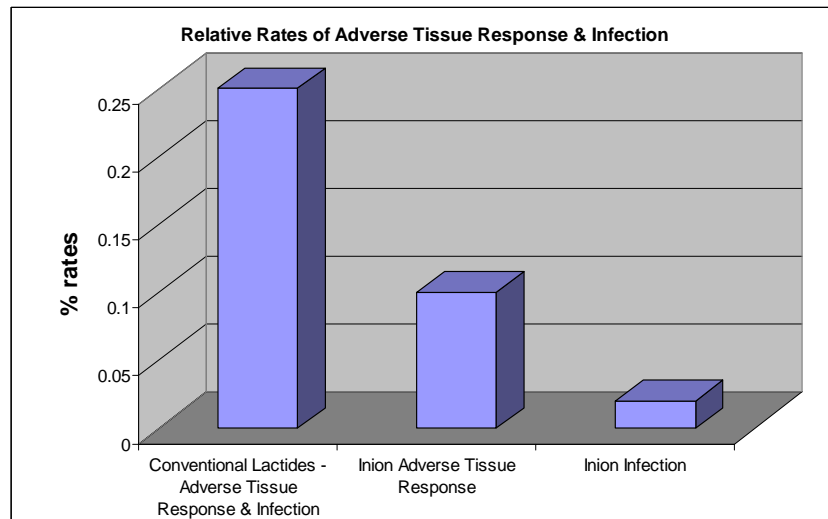


Fig.10. Relative rates of adverse tissue reaction and infections

Allowing for the relatively short (less than 5 years) history of Inion's clinical use, it might be considered premature to state conclusively why this is the case. However, there are several possible reasons including:

1. Higher degree of biocompatibility than previous biodegradable systems
2. Additional material components mean that not all the material degrades at the same rate, thereby reducing the load on the body's need to process degraded material at any one time

3. Reduced level of crystallinity of the polymer blend in comparison to polylactide-based implants

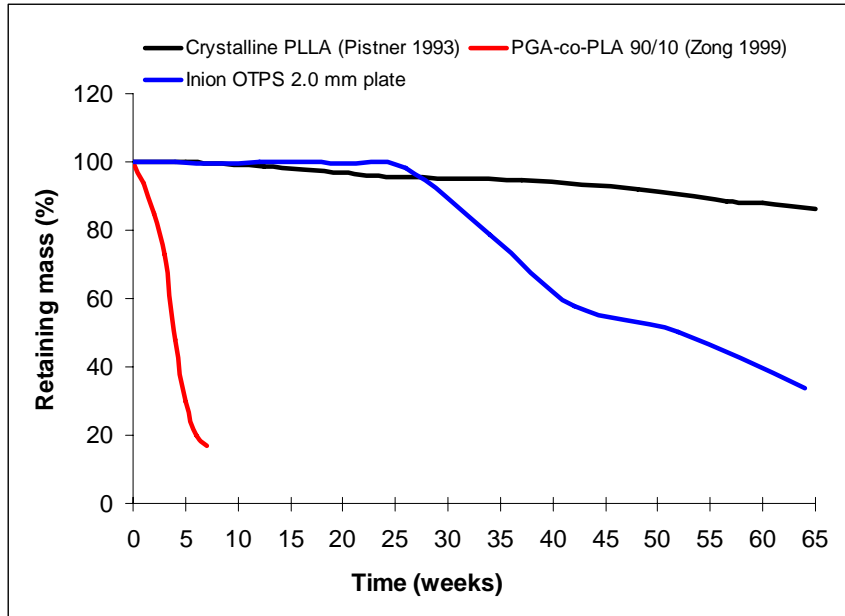


Fig. 11. Mass loss rate of fast degrading PGA-co-PLA 90/10 copolymer and slowly degrading crystalline PLLA in comparison to Inion OTPS 2.0 mm plate material.

4. Complete degradation of OPTIMA™ based products is typically 2-4 years.

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