# Poly (L-lactide) Osteosynthesis - development of bioresorbable bone plates and screws -

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CHAPTER 8

# SUMMARY, CONCLUSIONS AND PROSPECTIVE VIEW

## Summary

Internal fixation with metallic plates and screws is generally accepted as a reliable method for the fixation of maxillofacial fractures to achieve good bone healing. The most frequently applied plate systems consist of different types of dynamic compression plates and miniplates. Rigid fixation of fractures with compression allows the patient to exercise or even load the fractured bone. A major disadvantage, however, is that these metal devices have to be removed after fracture healing. The most important reason is bone resorption under the plate as a result of stress shielding. Inflammatory reactions due to loosening of the plate or to corrosion may occur. Metallic implants also cause backward scattering in patients who have to be irradiated because of a malignant tumor. Metal in the human body causes artifacts in computer tomography and magnetic resonance imaging. An other risk is the probability of patients becoming sensitized. This goes especially for alloys that bear nickel, cobalt and chromium. Titanium, and molybdenum are not believed to be haptens, whereas the immune role played by vanadium remains unclear. Carcinogenic potential of metallic osteosynthesis devices can not be ignored. Chromium, nickel, cobalt and some of their compounds are potent carcinogens in animals. Titanium is not known to be oncogenic in animals whereas the evidence concerning vanadium is still inconclusive. Possibly influenced by the oral implantology a tendency is noticeable to use plates and screws of titanium. It is supposed not to be necessary to remove these. Stress protection, however, still exists and transport of titanium oxide particles to the regional lymph nodes has been reported in relation with titanium implants. The application of plates and screws, manufactured out of biocompatible, bio-absorbable material with appropriate load-bearing properties and a sufficient rate of degradation could obviate the need for removal of plates and screws used for internal fixation of maxillofacial fractures or in orthognatic surgery. Only a few studies on resorbable plates and screws have been reported in the literature. A reliable system of resorbable plates and screws for practical use, however, is not yet available. (Chapter I).

In a survey of the literature the biocompatibility of poly(L-lactide) among other poly($\alpha$-hydroxy acids)is demonstrated. The apparent non-toxic, non-allergenic and non-carcinogenic products of hydrolysis can leave the body by normal excretory routes. L-lactic acid is a normal intermediate in the carbohydrate metabolism and shows up at the end of the anaerobic metabolism of glucose or glycogen. The biocompatibility of PLLA and the broad experience of the Pennings' Group (Department of Polymer Chemistry, University of Groningen, The Netherlands) with high molecular weight poly(L-lactide) are the reason that poly(L-lactide) was chosen as a base material for this investigation.

The preparation of this poly(L-lactide) was described by Leenslag et al. Polymerizations of L-lactide were performed after purification of the monomer (peak of melting 98°C) by recrystallization from toluene under $N_2$ atmosphere. Polymerizations were carried out in vacuum sealed ($10^{-7}$torr), silanized glass ampoules, at different temperatures (100 - 130° C). Stannous -2-ethylhexanoate was used as a catalyst (0.015 wt%). At the lowest temperature investigated (100°C) samples of PLLA with the highest intrinsic viscosities, up to 13 $dl.g^{-1}$, were synthesized (polymerization time 190 h). This method resulted in the synthesis of high molecular weight microporous poly(L- lactide) with very promising mechanical properties for use as internal fixation. (Chapter 2).

Bone plates and screws machined from this PLLA were used for fixation of two artificial mandibular fractures in sheep effected by a specially designed bone clamp. Clinical, radiographical and histological evaluation showed that fracture healing was uneventful without periosteal callus formation. Plates and screws of PLLA gave good stability over a sufficiently long period to enable normal fracture healing. Inflammatory or foreign body reactions were not observed. (Chapter 3).

The same type of biodegradable plates and screws was used for internal fixation of artificially created mandibular fractures in 6 dogs. Clinical and radiographical follow-up and examination under direct vision of the fracture site under general anaesthesia, showed that all fractures had healed without callus formation and without any complication. The plates or screws did not fail mechanically, although the tensile strength of the PLLA used is still less than that of stainless steel or any other metal. An explanation for their successful application may be the high value for impact resilience of this material. The proprioceptive mechanisms, however, that keep the dogs from maximal loading of their broken mandible, may also play a role. (Chapter 4).

The good results of the above described animal studies encouraged us to do a first clinical trial. Ten patients with unstable zygomatic fractures were treated with specially designed PLLA plates and screws. The results show that this method of fixation gives good stability over a sufficiently long period of time to enable undisturbed healing. Resorption of the plates and screws, however, progressed very slowly. (Chapter 5).



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In vitro and in vivo degradation of high molecular weight poly(L-lactide) used for internal fixation has been compared. Within 12 weeks, PLLA ($\bar{M}_v$ = 6,8 - 9,5 x $10^5$) exhibited a massive strength-loss ($\sigma_b$ = 68-75 MPa to $\sigma_b$ = 4 MPa) and decrease of $\bar{M}_v$ (90-95%). No differences between in vivo and in vitro degradation of PLLA were observed, except for bone plates used for fixation of fractures. These plates appeared to have a more rapid decrease in tensile strength than non loaded plates. After 3 weeks the loaded plates had lost already 67% of their initial strength of 650 N while the unloaded plates had lost only 30%. The strength loss after 6 weeks was 86% and 81% respectively. This, however, did not cause disturbed healing of mandibular fractures in 2 sheep and 6 dogs. In vitro experiments showed that extraction of residual catalyst, oligomers and monomer with ethyl acetate results in a more ductile PLLA exhibiting a lower rate of degradation. Ethyl acetate extracted PLLA samples retained their initial strength of 45 MPa for at least 12 weeks. Extraction of PLLA with ethyl acetate seems to be a promising technique to stabilize mechanical properties, resulting in a more ductile PLLA suitable for fracture fixation. In vivo tests with extracted PLLA are in progress. (Chapter 6).
Samples of the high molecular weight poly(L-lactide)(PLLA) ($\bar{M}_v$ = 9.0 x $10^5$), were implanted subcutaneously in the back of rats to study the tissue reaction to the PLLA and to follow the degradation process. The PLLA seems to follow the degradation pattern as it has already been described for other biodegradable poly($\alpha$-hydroxy acids). After pure hydrolysis up to about 104 weeks, phagocytic activity of macrophages is found at about 143 weeks. Full resorption of the PLLA could not be proven in this study. With exception of the early and final part of the implant period no acute or chronic inflammatory reaction has been observed during this study. Not any implant was rejected. Apparently it takes more than 3 years before the PLLA will be totally resorbed. (Chapter 7).

**Conclusions**

Considering the aim of this investigation the conclusion can be drawn that, at least for the longest follow-up period of 143 weeks, the PLLA used in this study proved to be biocompatible.
The tensile strength of the PLLA plates, used for fracture fixation was 50% (= 650 N) of the tensile strength of a 4-hole stainless steel Champy miniplate. The dimensions of the PLLA plates and screws had to be more coarse than those of miniplates and miniscrews. The PLLA plates and screws, however, proved to be strong enough and for a sufficiently long period to enable undisturbed fracture healing of mandibular fractures in 2 sheep, 6 dogs and of zygomatic fractures in 10 patients. The bone healing occurred without periosteal callus formation. In

our opinion, however, these good results do not suggest that at present the PLLA plates and screws are suitable for the fixation of every type fracture or osteotomy of the maxillofacial skeleton. Fixation of the mandibular fragments in particular is still not predictably safe. The required strength of plates and screws has to be determined not only by the loading forces a patient can develop but also by the nature and course of a fracture and the site at which plates and screws have to be applied. Especially in cases of oblique, complex or comminuted fractures, or when bridging of a defect is needed, plates and screws are much more loaded and in more directions than in case of single straight fractures as were used in the sheep and dogs. It is likely that, the higher the loading forces the PLLA plates and screws have to withstand, the more rapid the material will decrease in tensile strength due to stress cracking. This may result in premature failure of the osteosynthesis and thus in disturbed fracture healing. Considering the great variation in fractures it will be impossible to develop a simple system of resorbable plates and screws that will fully meet the specific demands of each fracture. In our opinion, however, it is possible and sound to use the generation of PLLA plates and screws as presented in this thesis for many fractures of the maxillofacial skeleton, including the mandible.

**Prospective view**

Running studies will give a definite answer about the time of total degradation of the PLLA used in this study. The most suitable sterilization method, the optimal dimensions and form of plates and screws, a practical method that enables bending of the plates and screws after heating and a suitable packing of plates and screws is investigated. Special attention is given that the properties of the PLLA are not affected negatively. The results of these studies will be reported in future papers. Future investigations should aim at higher initial mechanical properties of the resorbable materials which should remain stable for a longer period during fracture healing. Plates and screws will then be able to withstand more loading and are then suitable for more and other types of fractures of the human skeleton. Dimensions of plates and screws can be reduced which makes it possible to apply them to smaller bones and to sites where the anatomical situation asks for smaller plates and screws. Reinforcement of plates and screws with strong biodegradable fibers might be a solution. The ideal concept of plates and screws exists when the sum of the strength of the osteosynthesis and the strength of the healing fracture is sufficient to prevent redislocation and to make bone healing possible. The strength of the plate fixation can be lowered to zero as soon as the normal loadbearing properties of the fractured bone segment have been reached. The plates and screws should then be resorbed in a short period of time. The polymer chemist and the clinician will have to find ways to improve and evaluate biodegradable, biocompatible materials which meet the above-mentioned requirements. The future will show to what extent we are able to materialize this ideal; it is at least worth while trying hard.