CHAPTER 2

EFFICACY AND SAFETY OF BIODEGRADABLE
OSTEOFIXATION DEVICES IN ORAL AND MAXILLOFACIAL
SURGERY: A SYSTEMATIC REVIEW

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Abstract:
Background - The use of osteofixation devices should be evidence-based in order to secure uncomplicated bone healing. Numerous studies describe and claim the advantages of biodegradable over titanium devices as a bone fixation method.

Objective - To systematically review the available literature to determine the clinical efficacy and safety of biodegradable devices compared with titanium devices in oral and maxillofacial surgery. In addition, related general aspects of bone surgery are discussed.

Methods & materials - A highly sensitive search in the databases of MEDLINE (1966-2005), EMBASE (1989-2005) and CENTRAL (1800-2005) was conducted to identify eligible studies. Eligible studies were independently evaluated by two assessors using a quality assessment scale.

Results - The study selection procedure revealed four methodologically 'acceptable' articles. Owing to the different outcome measures used in the studies, it was impossible to perform a meta-analysis. Therefore, the major effects regarding the stability and morbidity of fracture fixation using titanium and biodegradable fixation systems were qualitatively described.

Conclusion & discussion - Any firm conclusions regarding the fixation of traumatically fractured bone segments cannot be drawn due to the lack of controlled clinical trials. Regarding the fixation of bone segments in orthognathic surgery, only a few controlled clinical studies are available. There does not appear to be a significant short-term difference between titanium and biodegradable fixation systems regarding stability and morbidity. However, definite conclusions, especially with respect to the long-term performance of biodegradable fixation devices used in maxillofacial surgery, cannot be drawn.

Abbreviations used in this paper are: CENTRAL, Cochrane Central Register of Controlled Trials; MeSH, Medical Subject Heading; VAS, Visual Analogue Scale; and W, weight.

Key words: Biodegradable, osteofixation, treatment, stability, morbidity, systematic review.

INTRODUCTION

Background
Maxillofacial traumatology and orthognathic surgery are major fields of oral and maxillofacial surgery. Internal rigid fixation systems are used for fixation and stabilization of osteotomized or fractured bone segments (35,36). Plates and screws are generally made of titanium and are currently regarded as the golden standard (43,73,74). Titanium fixation systems can be used safely and effectively (35,36). The intrinsic mechanical properties ensure that the device dimensions are kept within acceptable limits. The handling characteristics of titanium systems are simple and efficient (36). However, titanium devices also have disadvantages. These systems interfere with radiotherapy (37,41,42) and imaging techniques. Besides, titanium implants have been associated with complications such as growth restriction and brain damage (43), infection, and possible mutagenic effects (45).

A second intervention to remove the implants implies additional surgical discomfort, risks, and associated socio-economical costs (43,46-48). A plate removal percentage of 11.1% in Le Fort I osteotomies due to infection and plate exposure has been reported (49). In a retrospective study of 279 patients with isolated mandibular fractures, a plate removal percentage of 11.5% has been reported (50). In another study (32-34), 23 oral and maxillofacial surgeons were interviewed regarding removal of mini-plates. The authors concluded that the plate removal percentage varies between 5% and 40%

Biodegradable osteofixation systems have the possibility to degrade, thus preventing the need for a second intervention (35,36). Another advantage of biodegradable devices is their radiolucency, implying good compatibility with radiotherapy and imaging techniques (42,53,54). Besides, osteoporosis can be prevented due to the gradual transfer of functional forces to the healing bone during the disintegration process of biodegradable devices (55,56).

Since the introduction of biodegradable devices in 1966 (57), the development of their mechanical properties and degradation characteristics has been extensive (58). Numerous in vitro, animal, and clinical studies have been published about positive (59-65) as well as negative results (66-69). Despite the supposed advantages of biodegradable osteofixation devices, these systems did not replace the titanium systems and are currently applied in only limited numbers (43,70). The mechanical properties are less favourable and ultimate resorption has not been proven (71). Another significant factor of the limited use is the resistance by surgeons to modify their conventional, well experienced, treatment techniques (72). The major drawback for general use of biodegradable devices is the lack of clinical evidence.
CHAPTER 2

GENERAL ASPECTS OF BONE SURGERY

Various \textit{in vitro} and \textit{in vivo} studies must be performed before innovative interventions can be used safely and effectively in the clinic (75). Studies that have been important for understanding the behaviour and characteristics of biodegradable and titanium osteofixation systems are reviewed in the subsequent sections.

Mechanism of bone healing

Fractured bone or locally damaged bone causes disruption of many blood vessels. This disruption results in local haemorrhage followed by the formation of a blood clot. Osteocytes at both sides of the fracture die due to deprivation of blood perfusion. Restoration of the fracture area starts with the clearance of the blot clot, death cells and bone matrix under the influence of revascularization. Periosteum, endosteum and surrounding tissues respond by cell proliferation. The tissue that arises between both fracture ends, and serves as a temporary bridging, is called callus. Its composition varies with site and circumstances (76;77). Cartilage is formed in parts of the callus that are not sufficiently saturated with blood. Subsequently, cartilage is transformed into bone by enchondral bone formation. If sufficient blood saturation occurs, a direct network of bars of plexiform bone is formed by endosmale bone formation. As a strong bony callus arises, it can be subjected to normal tension- and compression forces (78).

Resorption and formation of bone is a dynamic and continuously changing process, which has an equilibrium defined by internal factors (mainly hormones) and external factors (mainly mechanical forces). Inadequate immobilization during the healing process causes disruption of the revascularization process. This results in the formation of a fibrous callus followed by an incomplete healing of the fracture. Too rigid fixation, on the other hand, may also cause problems. Lack of normal functional stimuli in the final stages of bone healing will inhibit the formation of new bone, while the resorption of bone still proceeds (79;80). This could result in local osteoporosis (76;77;81).

Objectives

The use of biodegradable osteofixation devices should be evidence-based in order to secure uncomplicated bone healing (73). Numerous studies describe and claim the advantages of biodegradable over titanium devices as a bone fixation method (60;74). In the present study, the currently available literature regarding the clinical efficacy and safety of biodegradable osteofixation devices compared with titanium osteofixation devices in oral and maxillofacial surgery was systematically reviewed. The research question was phrased as follows: “is there a difference in stability and morbidity regarding the fixation of bone segments with biodegradable or titanium fixation devices in orthognathic and trauma surgery?” The available literature regarding current relevant aspects of bone surgery will also be discussed.

Mechanical aspects

Various muscles of the maxillofacial skeleton exert a wide variety of forces in different directions. This implies that it is difficult to estimate the required mechanical properties of a fixation system. Decisions regarding the required plates and screws are rarely evidence-based (82). The primary mechanical strength and stiffness of biodegradable osteofixation devices are less favourable compared to their conventional titanium counterparts. This is inherent to the use of biodegradable polymers. However, the question is whether their mechanical properties are sufficient for resisting the local deforming forces (83).

The main objective in orthognathic and trauma surgery is fast, anatomical and painless functional reunion of bone segments (84). Revascularization plays an essential role in this process (78;85). Titanium plates and screws are intrinsically small, strong, and biocompatible (37). As a result, the main objectives regarding fixation management can be met. The rigidity of titanium fixation systems might also be disadvantageous. The system probably inhibits the transfer of functional forces to healing (or healed) bone, which may result in osteoporosis as was mentioned in the previous section (55;56;81). By contrast, the strength and stiffness of biodegradable fixation systems decrease with time because of the disintegration of the polymer chains, in this way ensuring progressive loading during the subsequent stages of bone healing. To compensate for the less favourable mechanical properties of biodegradable devices, manufacturers increase their dimensions. This may interfere with tensionless wound closing, making the wound area more prone to infection. Enlarged dimensions restrict easy application in small areas which are difficult to access (e.g. paediatric surgery) (40). These factors imply that the field of application of biodegradable devices, in particular regarding bone fixation in the maxillofacial area, is restricted (43), whereas titanium systems may be applied almost anywhere.

Despite the disadvantages of the enlarged dimensions of biodegradable systems as mentioned above, several patient series have been published regarding the successful use of biodegradable fixation systems applied in different (e.g. heavy load bearing) situations (e.g. mandibular fractures and bilateral sagittal split osteotomies). The treatment of 1883 patients, in whom cranio-maxillofacial deformities were fixed with the biodegradable LactoSorb fixation system, was evaluated in a recent study (60). Regarding to the rapidly growing cranial vault, the authors noted, that fewer potential complications occurred using the biodegradable system compared with the titanium plates and screws. The BioSorb FX biodegradable fixation system has been found to be an appealing alternative for titanium fixation systems regarding orthognathic, trauma and cancer surgery, corrective cranioplasty, and fixation of bone grafts in another recent study (86).

Considering the biomechanical aspects, selecting plates and screws is not always that straightforward. The surgeon should consider the (1) local deforming forces and (2) which system (biodegradable or titanium) could optimally resist the deforming forces (87), and in what configuration (number of screws in both fracture ends).
Biocompatibility and resorption aspects

Biocompatibility refers to how a material elicits a host response in a specific situation. Tissue responses to implanted material are numerous and complex. The term biocompatibility also describes aspects of interactions between implanted material and the host (88;89). The process of removal of a material by cellular activity and/or dissolution in a biological environment, is called resorption (90). Degradation is the disintegration of material into smaller parts. Biocompatibility, resorption and degradation are closely interrelated. The biocompatibility of biodegradable internal fixation devices is strongly influenced by the degradation and resorption behaviour of the polymers used (75;91). These systems are made of different polymers (e.g. poly(L-lactide), poly(D-lactide), poly-glycolide, polydioxanone, trimethylene carbonate). These materials degrade and resorb in two phases (92). During the first phase, water molecules hydrolyze the long polymer chains into shorter fragments. The molecular weight and the polymer strength decrease during this process. The second phase consists of a physiologic response of the body in which macrophages phagocyte and metabolize the short fragments which subsequently enter the citric acid cycle (93-95). Water and carbon dioxide remain and are subsequently excreted from the body, mainly through respiration. The mass of the biomaterial rapidly disappears during phase two (57;96). In addition, enzymes are supposed to play a considerable role in the degradation (97;98).

Degradation and resorption processes of biodegradable polymers frequently elicit adverse tissue responses. This represents an inherent biologic tissue response (75) as occurs with every implanted material (67). Regarding orthopedic surgery, the general incidence of adverse tissue responses using fixation devices made of poly-glycolide varies from 2.0 to 46.7% (75). The incidence of adverse tissue responses is generally lower for plates and screws made of poly-lactide (75). The time between implantation and appearance of adverse tissue responses varies from 10-12 weeks (48;67;99) to 4-5 years (66;100;101) for respectively poly-glycolide and poly-lactide.

The clinical characteristics of the adverse tissue responses vary from a local swelling without signs of inflammation (66) to a suddenly emerging painful, erythematous, fluctuating papule which reveals a sinus discharge of liquid remnants of disintegrated implant materials (75). Radiographs obtained at the time of manifestation show osteolytic changes around the implanted material in 50% of the patients (68;102). The histopathologic picture has been characterized by an abundant polymeric debris, being surrounded by mononuclear phagocytes and multinucleated foreign-body giant cells (67;68;103;104). The possible risk factors for developing adverse tissue responses seem to be associated with the extent of vascularization, which inherently depends on the site of implantation. Moreover, the implant design appears to affect the response rate. Cylindrical pins and rods show a lower incidence of adverse tissue responses than screws. Foreign-body response rates seem to be independent of patients’ age and gender as well as the implanted polymer volume. The long-term ultimate biocompatibility and resorption of biodegradable plates and screws have frequently been investigated, yet remain to be established (75;105). Researchers have reported varying *in vivo* results. A recent histologic study (106) reported complete resorption of Resorb® X and LactoSorb screws after 12 and 14 months, respectively, found by the use of a fluorescence microscope. However, bone re-modelling was not completed after 26 months. The degradation process of biodegradable implants has also been investigated through MRI (107). The authors concluded that no complete resorption had occurred after 34 months.

Based on these findings, large-scale, long-term controlled clinical trials can be recommended to verify the ultimate biocompatibility and resorption characteristics of biodegradable implants and to establish evidence-based treatment methods.

Characteristics of “ideal” osteofixation devices

Considering the aspects mentioned in the previous sections, an ideal osteofixation device should (82;92): (1) be fabricated and designed with appropriate initial strength to meet the bio-mechanical demands, (2) not cause tissue responses necessitating device removal, (3) be easy to use and handle, (4) be cost-effective, and (5) be compatible with radiotherapy and imaging techniques. Regarding biodegradable osteofixation devices, the following aspects should additionally be incorporated: (6) degrade in a predictable fashion and allow for safe progressive loading during each stage of bone healing and (7) disappear completely.

**CONTROLLED CLINICAL STUDIES – A SYSTEMATIC REVIEW**

**METHODS**

**Literature search**

To identify studies on the efficacy and safety of biodegradable osteofixation devices, a highly sensitive search was carried out in the databases of MEDLINE (1966-2005) and EMBASE (1989-2005). The search was supplemented with a systematic search in the ‘Cochrane Central Register of Controlled Trials’ (CENTRAL) (1800-2005). Free text words and the applied thesaurus (MeSH) regarding the search strategy are summarized in Table I. Several experts in the field of biodegradable osteofixation devices were contacted to ensure eligible studies were not overlooked. Moreover, leading oral and maxillofacial journals were screened for missing articles. To complete the search, reference lists in the obtained literature were checked for additional relevant articles. No language and time restrictions have been included in the search strategy.

The search strategy was focused on three aspects: (1) terms to search the ‘health’ condition of interest (i.e. fracture and osteotomies of the maxillofacial skeleton); (2) terms to search for the intervention(s) evaluated (i.e. biodegradable and titanium osteofixation device(s)); and (3) terms to search for the types of study design to be included (i.e. clinical controlled trials) (108). Free text words and MeSH terms were formulated precisely, resulting in a scrupulous primary exclusion of ‘non clinical trials’ as well as studies which are rarely topic related.
Study selection

The relevance of studies was evaluated by a first selection based on title and abstract. Since the research question focuses on the efficacy and safety of biodegradable osteofixation devices in comparison with titanium devices, only controlled clinical trials (CCT) were considered for inclusion in the systematic analysis.

The review was focused on studies concerning the treatment of fractures and the performance of osteotomies of the maxillofacial skeleton (i.e. Le Fort I, Le Fort II, and Le Fort III fractures and osteotomies, cranial fractures, malar fractures, mandibular fractures, and sagittal split osteotomies of the mandible). Studies involving children were also considered for inclusion. Disagreement about whether or not a study should be included was resolved by a consensus discussion. Full-text documents were retrieved of all relevant articles. The study selection procedure is outlined in figure 1.

Table I. Search strategy

<table>
<thead>
<tr>
<th>Step</th>
<th>Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>surger* or fracture* or trauma* or reconstruction* or orthoped* or injur*</td>
</tr>
<tr>
<td>#2</td>
<td>explode &quot;Maxillofacial-Injuries&quot;/ all subheadings</td>
</tr>
<tr>
<td>#3</td>
<td>explode &quot;Facial-Bones&quot;/ all subheadings</td>
</tr>
<tr>
<td>#4</td>
<td>maxillofacial* or craniomaxill* or craniofacial*</td>
</tr>
<tr>
<td>#5</td>
<td>jaw* or mandib* or maxill*</td>
</tr>
<tr>
<td>#6</td>
<td>#1 and (#2 or #3 or #4 or #5)</td>
</tr>
<tr>
<td>#7</td>
<td>&quot;Absorbable-Implants&quot;/ all subheadings</td>
</tr>
<tr>
<td>#8</td>
<td>&quot;Bone-Plates&quot;/ all subheadings</td>
</tr>
<tr>
<td>#9</td>
<td>&quot;Bone-Screws&quot;/ all subheadings</td>
</tr>
<tr>
<td>#10</td>
<td>&quot;Internal-Fixators&quot;/ all subheadings</td>
</tr>
<tr>
<td>#11</td>
<td>plate* or screw* or miniscrew* or miniplate* or implant* or osteosynth* or osseointegrat* or osteofixation* or osteotom* or internal fixation</td>
</tr>
<tr>
<td>#12</td>
<td>bioreabsorb* or biodegrad* or bioabsorb* or bioadsorb* or absorb* or resorb* or adsorb*</td>
</tr>
<tr>
<td>#13</td>
<td>(#7 or #8 or #9 or #10 or #11)</td>
</tr>
<tr>
<td>#14</td>
<td>((clinical* in ti,ab) and (trial* in ti,ab)) or (PT:MEDS = clinical-trial) or (<em>Clinical-Trials</em> / all subheadings)</td>
</tr>
</tbody>
</table>

Inclusion and exclusion of studies

To identify eligible studies suitable for methodological appraisal, relevant studies underwent a second selection procedure based on the completeness of the report. The following implant-related outcome measures should be evaluated:

- union/non-union of the fracture within the follow-up period;
- wound healing/infection;
- intervention with biodegradable as well as titanium osteofixation device;
- proper (control) group;
- diagnoses and indications for treatment must be well established by clinical and radiographic evaluation.

Studies, meeting the above-mentioned criteria, were subjected for further methodological appraisal.

Quality assessment of studies

A quality assessment of the remaining studies was performed to control the influence of bias in a systematic analysis, to gain insight into potential comparisons, and to guide interpretation of findings (108). A registered methodologist and oral and maxillofacial surgeon (BS) as well as a PhD resident (GJB) assessed the methodological quality with the ‘quality of study tool’ developed by Sindhu et al. (109). The ‘quality of study tool’
consists of 53 items in 15 dimensions and is outlined in Table II. Each dimension has a specific weight \( W \). The included articles revealed an independent score by the two observers according to the 15 dimensions (range 0-100). Agreement regarding the weight of the individual sub-dimensions and the required minimum ‘methodological’ values for each dimension was reached in a consensus meeting. Based on these minimum values, summation yielded a threshold value, which in this study was 54.

If feasible, a meta-analysis was carried out provided that the primary outcome measures (defined in the individual studies) could be meaningfully combined in an overall effect-size.

**Statistical analysis**

The degree of agreement between the two observers regarding eligible studies before the consensus meeting is expressed as a percentage of agreement of unweighted Cohen’s kappa. Where applicable, Cochrane Review writing software (RevMan) was used to calculate the overall effect sizes by means of the random-effects model.

**RESULTS**

The MEDLINE, EMBASE and CENTRAL search identified 122, 29 and 87 publications, respectively. Systematic assessment of these 238 articles according to the specified ‘eligibility’ criteria revealed 5 possible eligible publications. Inclusion of a ‘titanium control group’ appeared to be the limiting criterion in this selection, however essential for answering the research question. Inclusion of a control group and, preferably, random assignment are major aspects for controlling unknown influences and possible confounders (108;110). Checking references of relevant articles and contacting experts did not reveal additional articles. Methodological assessment of the 5 eligible publications revealed 4 methodologically ‘acceptable’ articles. One article was excluded because of inadequate reporting of the methods and results (1). Inter-assessor agreement on the methodological quality of each study was 96% (unweighted kappa, 0.90; 95% CI: 0.85 to 0.96). Disagreements were generally caused by slight differences in interpretation and were easily resolved in a consensus meeting.

Three studies used randomization to allocate patients to the treatment groups (2;4;5). One study allocated patients consecutively (3). LactoSorp® plates and screws (W. Lorenz Surgical, Jacksonville, Florida) were used to fix bone segments in two studies (2;3). The LactoSorp® fixation system has a copolymer composition of 82% L-lactide and 18% glycolide. Ferreti et al. (2002) studied mandibular splits fixed with three bi-cortical screws whereas Norholt et al. (2004) investigated the stability and relapse of Le Fort I osteotomies. One other methodologically ‘acceptable’ study (4) investigated the fixation of different osteotomies using BioSorb FX plates and screws (Linvatec Biomaterials Ltd.). The BioSorb FX fixation system is made of self-reinforced (70% L-lactide, 30%D-lactide) poly lactic acid. The most recent study (5) investigated the changes in condylar long axis and skeletal stability after bilateral sagittal split ramus osteotomies using 100% poly-L-lactic acid plates and screws (Fixsorb®-MX, Takiron Co., Osaka, Japan).
Because of the different effect-sizes used in the methodologically ‘acceptable’ studies, it was impossible to perform a meta-analysis. Therefore, the major effects regarding the stability and morbidity of fracture fixation are qualitatively described in the subsequent sections.

**Stability**

Stability of fixed bone segments is an important outcome measure since the aim of fixation systems is to establish a functional, anatomical and pain-free reunion of bone segments. In the four included articles, the stability of the osteotomized segments was assessed with different methods.

Cephalometric analysis was used in three of the four included studies to accurately assess the skeletal stability (2;3;5). Regarding bilateral sagittal osteotomies (5), the outcome measures SNA, SNB, and ANB did not significantly differ for the titanium and PLLA group. The interincisor angle, occlusal plane angle, mandibular length, overbite, overjet, and convexity were also similar in both groups. The location of the pogonion neither showed a significant difference. In the second study (2), Le Fort I osteotomies fixed with biodegradable plates and screws revealed a significant difference in vertical dimension of the upper jaw (mean difference 0.6 mm) after 6 weeks post-operatively. The osteotomies fixed with titanium plates and screws did not present a significant difference. The authors (2) concluded that the statistically significant difference of the vertical dimension in the biodegradable group (LactoSorp®) was not clinically relevant. Ferretti et al. (3) evaluated the relapse (skeletal stability) of bilateral sagittal osteotomies. The mean transposition of the mandible fixed with three bi-cortical screws was 4.7 (sd = 1.3) and 5.5 (sd = 1.7) millimeters for respectively the titanium and biodegradable group. The mean relapse was 0.25 (sd = 1.25) and 0.83 (sd = 1.25) millimeters after 6 weeks post-operatively. No difference in this respect was revealed between the biodegradable and the biocompatible fixation. In all patients, the maxilla became stable and firm in the sixth week, and no further mobility could be detected during the follow-up period.

**Morbidity**

The morbidity of osteofixation devices is evaluated in all of the included studies (2-5). Various aspects were evaluated, including pain on chewing, maximum mouth opening range (MMOR), and temporomandibular disorder symptoms. Pain on post-operative chewing revealed lower VAS scores compared to pre-operative chewing in both groups. The VAS scores between both groups were nearly similar. Maximum mouth opening range did not differ significantly between the two groups.

Table III. General characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Design trial</th>
<th>Type of treatment</th>
<th>Type of fixation</th>
<th>Patients</th>
<th>Quality score</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueki et al., 2005</td>
<td>Randomized</td>
<td>Mandibular split</td>
<td>Titanium Fixorb® MX</td>
<td>20/20</td>
<td>77</td>
<td>No difference regarding pain on chewing and MMOR® More TMD® symptoms in degradable group</td>
</tr>
<tr>
<td>Norholt et al., 2004</td>
<td>Randomized</td>
<td>Le Fort I osteotomy</td>
<td>Titanium LactoSorb</td>
<td>30/30</td>
<td>82</td>
<td>Very low morbidity Tendency for impaction in titanium group, no impaction in the degradable group</td>
</tr>
<tr>
<td>Cheung et al., 2004</td>
<td>Randomized</td>
<td>Le Fort I osteotomy</td>
<td>Titanium BioSorb FX</td>
<td>30/30</td>
<td>79,5</td>
<td>No significant difference regarding clinical stability and clinical morbidity</td>
</tr>
<tr>
<td>Ferretti et al., 2004</td>
<td>Controlled</td>
<td>Mandibular split</td>
<td>Titanium LactoSorb</td>
<td>20/20</td>
<td>68</td>
<td>No significant difference regarding clinical stability and clinical morbidity</td>
</tr>
</tbody>
</table>

# MMOP, Maximum Mouth Opening Range, TMD, TemporoMandibular Disorder.
1. Arranged according the publication date
2. Follow up 1 year
3. Maxillary subapical osteotomy
4. Mandibular subapical osteotomy
5. Mandibular body osteotomy
The number of symptomatic joints in the titanium group was significantly less compared to the PLLA group. General clinical aspects (infection, wound dehiscence, plate exposure and palpability of plates and screws) are objectively assessed in two included studies (2,4). The inflammatory responses gradually decreased with time. The first study (2) reported wound dehiscence in 1 patient in the biodegradable group whereas the second study (4) revealed wound dehiscence in 3 patients in the titanium group (10%) and in 2 patients in the biodegradable group (6.7%). No complications occurred as result of the dehiscence. The palpability of biodegradable plates and screws decreased with time in both studies, while the palpability of titanium plates and screws increased. In the study of Cheung et al. (4), plate exposure affected 1.02% and 1.21% of the patients in the titanium group and biodegradable group respectively whereas Norholt et al. (2) discussed one patient in the biodegradable group with plate exposure (4.2%). One included study (4) reported the removal of 3 titanium (1.53%) and 6 (3.36%) biodegradable plates (as a percentage of all plates and screws used). Ferreti et al. (3) reported briefly the clinical appearance of the surgical ‘sites’. They appeared to be abnormal with respect to the evaluation criteria (swelling, discharge, pain, or discoloration of the mucosa and skin) during the post-operative 12 months. The general characteristics, results and conclusions of the included studies are summarized in Table III.

GENERAL DISCUSSION

Mechanical aspects
Regarding the mechanical aspects, the selection of an adequate fixation system remains difficult due to varying local situations (fracture line(s), anatomy, patients and muscle activity). To guide decisions regarding the required fixation system in different clinical situations, a comparison of the initial mechanical strength and stiffness of biodegradable and titanium systems could be valuable. Moreover, the surgeon is predominantly interested in the device (functional unit) characteristics of a fixation system rather than in the material characteristics. The variability of biodegradable osteofixation systems (i.e. co-polymer composition and geometry) makes a well-funded selection difficult (82). Besides the initial mechanical characteristics of osteofixation systems, the torsion strength and stiffness of the screws are important. The screws fix the osteofixation plate against the bone segments and prevent sliding of the bone segments and the fixation system relative to each other. This ensures adequate stabilization of the bone segments. Screws also generate inter-fragmentary compression to stabilize mandibular splits, which will enhance fracture healing. The torsion strength and stiffness of the biodegradable screws are less favourable (111) compared to titanium screws, which have been reported as a disadvantage by several authors (111,112). Moreover, biodegradable polymeric screws relax when a force is continuously applied (111). These aspects may result in decreased fracture stability and possible compromised fracture healing.

Biocompatibility and resorption aspects
Long-term ultimate biocompatibility, as is the goal of any implanted material, is difficult to establish. Despite considerable clinical experience of fracture fixation using biodegradable materials, long term clinical studies are scarce. Moreover, studies reporting the long-term complications (66;67;101) probably represent one end of a continuous spectrum of biological responses. The majority of the cases pass sub-clinically and remain unnoticed despite the elicitation of a (small) biological host response as is the case with every implanted material (67). The degradation and resorption characteristics as well as the possibility to develop adverse tissue responses, depend largely on the nature of the implanted materials. Polylactide is a major component of the biodegradable fixation devices and the time to elicit a considerable host response is 4 to 5 years (66;100;101;113). Therefore, studies reporting the biocompatibility and degradation characteristics regarding this material should last for at least 5 years (114). However, few laboratory animals live long enough and, consequently, long-term biocompatibility experiments are difficult to design. The development of adverse tissue responses seems to originate from several different physiologic and chemical processes. Crystalline remnants and a decrease of pH(115) during degradation are probably responsible for the adverse effects of biodegradable polymers, although the local tissue tolerance and the local clearing capacity seem to be important aspects as well (67;100;116,117). The rate of crystalline remnants and decrease of pH are partly determined by the molecular structure of the biomaterial (118). Amorphous polymers degrade faster than crystalline polymers, resulting in a rapid decrease of the pH. Crystalline polymers may remain in situ for decades (92). A high blood flow rate is an essential prerequisite for successful implantation of biodegradable fixation materials, since adequate blood flow secures sufficient removal of degradation products preventing a decrease in pH (114). PDLLA implants enriched with calcium phosphates have been investigated in rats to prevent a local decrease in pH (119). The control group received pure PDLLA implants. The PDLLA implants enriched with calcium phosphates showed an increased tissue response after 72 weeks. The authors concluded that the ‘enriched’ implants are not suitable for clinical use.

Clinical aspects
The major objective of this systematic review was to evaluate the clinical efficacy and safety of biodegradable osteofixation devices in comparison with titanium osteofixation devices used in oral and maxillofacial surgery. Unfortunately, we cannot draw any firm conclusions regarding the fixation of traumatically fractured bone segments, owing to the lack of controlled clinical trials. Studies using two randomized treatment groups are difficult to design and not (yet) available. Regarding the fixation of bone segments in orthognathic surgery, only a few controlled clinical studies (2-4) are available. There does not appear to be a significant difference in outcome between titanium and biodegradable fixation systems. Definite conclusions regarding the long-term performance of biodegradable fixation devices used in maxillofacial surgery cannot be drawn.
CHAPTER 2

The methodologically ‘acceptable’ studies contain much heterogeneity. The studies individually defined the outcome measures for stability and morbidity. Moreover, the treatment modalities performed in these studies were different (Le Fort I, sagittal split osteotomies and various osteotomies). The biodegradable fixation system (LactoSorb) used, was similar in only 2 studies (2,3). Because of the heterogeneity, pooling of outcome measures was not meaningful.

A primary way to establish whether a fixation system has functioned successfully is to assess the extent of clinical mobility. However, objective mobility measurements in the maxillofacial skeleton are difficult to perform. One study reports the stability according to a nominal scale: none-, slight- and gross mobility (2) while another study reports the mobility according to a binary scale: immobility versus mobility (4). One methodologically ‘acceptable’ study did not even report the extent of mobility (3). In our opinion, it is essential to report the extent of mobility when investigating the clinical efficacy and safety of biodegradable osteofixation systems. Therefore, we advise the use of a binary scale. The aim of an osteofixation device is to achieve functional, pain-free re-union within a reasonable period of time (6 weeks) (120). Compromised healing or slight mobility is considered a non-union. The most recent study (5) applied post-operative inter-maxillary fixation (IMF) for 2 weeks to prevent adverse alterations of the post-operative occlusion. The authors did not know whether the PLLA plates were strong enough to stabilize the bone segments. Today, IMF is not the state of art and thus, in our opinion, improper to apply when comparing the skeletal stability of bilateral sagittal split osteotomies fixed with titanium or PLLA plates.

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One of the major drawbacks of the reviewed literature is the lack of sufficient follow-up. Three of the included studies (2,3;5) followed their patients only 1 year post-operatively. Another included recent study (4) followed a few of their patients for 2 years (6 out of the titanium group and 7 out of the biodegradable group) and 24 patients in both groups were evaluated for 1 year. In our opinion, the follow up periods are too short to draw definite conclusions as to whether these biodegradable implants could serve as a safe and reliable fixation method on the long term. Many authors (60;70;86) have reported patient series with longer follow up periods. As mentioned earlier, since these patient series lack a control group, an adequate comparison with titanium fixation devices has not been made in these studies. Future clinical trials should, from a biocompatibility and resorption point of view, evaluate patients for at least 5 years as mentioned in the previous section (4.2).

The onset of infections seems to differ for fixation of fractures with titanium or biodegradable devices. One included study (4) reported that the infections in the biodegradable group were diagnosed after 6 weeks, 3 months, and 6 months, while those in the titanium group were diagnosed after 2 weeks, 6 weeks, and 3 months. Another included study (2) reported that 1 infection in the titanium group was diagnosed after 1 week, whereas 2 infections in the biodegradable group were diagnosed after 6 months. These clinical findings suggest that the onset of infections tend to occur later in the biodegradable groups. The authors could not explain this tendency, although one (2)

suggested that it could be caused by the ongoing degradation of the plates and screws. The known causes of infection are loosened screws and wound dehiscence (4). In one of the included trials, the authors (4) report the infection percentages in terms of individual plates (1.53% in the titanium group and 1.82% in the biodegradable group) and in terms of individual patients (10% in each group). In the discussion, the authors advocate that it is more reasonable to use the plate and screw as the unit for calculation, because an infection will occur if any single component fails. However, in our opinion it is more reasonable to use the individual patient infection-percentages to calculate the percentage of infection. After all, infection percentages in terms of individual patients will gain more insight in the extent of actual re-operating procedures. Moreover, cost-effectiveness analyses are more meaningful using infection percentages in terms of individual patients. However, cost-effectiveness analysis regarding the use of biodegradable fracture fixation devices were not reported in any of the included trials (2-5).

SUMMARIZING AND CONCLUDING REMARKS

The implications for the clinical applicability of biodegradable osteofixation systems on the long-term remain inconclusive. There is evidence available from randomized controlled trials to support the conclusion that there is no significant difference between biodegradable and titanium osteofixation devices with regard to short-term clinical outcome, complication rate and infections in the area of orthognathic surgery. Re-operation rates do not significantly differ in the biodegradable and titanium group. A sufficient follow up (of at least 5 years) is necessary in order to draw decisive conclusions regarding the use of biodegradable implants in oral and maxillofacial surgery. Until then, we can conclude that decisions with respect to plate and screw size, number of plates and screws, and biodegradable or titanium must be made on individually relevant aspects. Relevant factors include the nature of the injury, technical considerations, and the experience of the surgeon.

Since this systematic review has some implications for future research, there is an urgent need for sufficiently powered, high quality and appropriately reported randomized controlled trials with respect to biodegradable osteofixation devices versus non-degradable osteofixation devices for well-defined maxillofacial fractures and osteotomies. Future studies should include a cost-effectiveness analysis in which hospital admission costs, surgical costs (material), and the costs associated with sick leave of the patients should be analyzed.

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