Biodegradable plates and screws in oral and maxillofacial surgery
Buijs, Gerrit Jacob

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BIODEGRADABLE AND TITANIUM FIXATION SYSTEMS IN ORAL AND MAXILLOFACIAL SURGERY: A RANDOMIZED CONTROLLED TRIAL

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Submitted
Abstract:  
**Background** - Metallic plates and screws are used for immobilization of bone fragments in trauma and orthognathic surgery. Some authors advocate the removal of metallic plates and screws because of potential adverse reactions. A second operation to remove osteosynthesis following bone healing is reported in 5 - 40% of the cases. This is highly undesirable in terms of cost-effectiveness, patient comfort, healthcare quality and risk of complications. Biodegradable fixation systems could reduce or even delete the problems associated with metallic systems since removal is not necessary.  
**Aim** - The aim of this study was to establish the effectiveness and safety of biodegradable plates and screws as a potential alternative to metallic ones.  
**Materials & Methods** - This multi-centre randomized controlled trial was conducted from December 2006 to July 2009. Included were patients who underwent mandibular- and Le Fort I osteotomies and those with fractures of the mandible, maxilla, and zygoma. The patients were assigned to a titanium control-group (KLS Martin) or to a biodegradable test-group (Inion CPS). The primary outcome measure was 'bone healing 8 weeks after surgery'.  
**Results** - The Intention To Treat analysis (ITT) of 111 patients in the titanium group and 112 patients in the biodegradable group yielded a non-significant difference. In 25 patients (22%) who were included in the biodegradable group, the surgeon made the decision to switch to the titanium system per-operatively.  
**Conclusion & discussion** - Despite the ‘non inferior’ primary outcome result, the benefits of using biodegradable systems (less plate removal operations) should be demonstrated during a follow-up of minimally 5 years, especially when the large number of patients for whom it was per-operatively decided to switch from the biodegradable system to the conventional titanium system, are taken into account.

**INTRODUCTION**

Essential prerequisites for the bone healing of fractures and osteotomies include sufficient vascularization, anatomical reduction, and immobilization of bone segments (7;10). Up to the seventies, fractures and osteotomies were fixed with (stainless) steel wires supported by InterMaxillary Fixation (IMF) to achieve bone healing and restore occlusion. The use of IMF during the healing period of 6 weeks is very uncomfortable. Besides, it immobilizes the temporomandibular joints resulting in cartilage degeneration (140). The last four decades, immobilization of bone fragments can be obtained using metallic plates and screws without applying IMF (125;126). This allows patients to load functionally their masticatory system immediately following surgery. The currently available metal plating systems have the advantage of combining excellent mechanical and handling properties. A disadvantage of the use of metallic plates and screws is that they remain during life. This results in several potential adverse effects such as: (1) sensitivity to hot and cold stimuli (129), (2) palpability of the plates, (3) possible growth disturbance or mutagenic effects (37;41;43-45), and (4) interference with imaging or radio-therapeutic irradiation techniques (37;41;127). As a consequence, some authors remove the implants in a second operation following bone healing. This has been reported in 5 - 40% of the cases (32-34). Because of this apparent disadvantage, there is a continuous drive to explore the use of biodegradable fixation systems (4). These systems could reduce or even delete the problems associated with metallic systems (74). This would be highly desirable from the viewpoint of cost-effectiveness, patient comfort, healthcare quality, and risk of complications due to plate removal. However, adverse tissue reactions to degradation products have been reported (66;67;100;114). Moreover, biodegradable systems are mechanically less favourable than metallic systems, which can result in insufficient bone healing.  
Many case reports and case series have been published reporting the clinical performance of a variety of commercially available biodegradable systems used for different indications. These studies show various outcome results (48;64;70;141-143). Only a few controlled trials have been published on this subject (2-4;144), which have previously been summarized and analyzed in a systematic review (122). The results were inconclusive, mainly because of the lack of sufficiently powered and appropriately designed trials and heterogeneity among the included studies. Given the lack of adequate evidence as well as the obvious advantages of using biodegradable plates and screws for the patient, and society, there is a need for well-designed randomized controlled trials of sufficient size.  
The aim of this study was to establish the effectiveness and safety of biodegradable plates and screws as an alternative to metallic ones. Therefore, we tested the null-hypothesis that the performance of the Inion CPS biodegradable system is inferior to the titanium system regarding bone healing following treatment of mandibular, maxillary (Le Fort I), and zygomatic fractures as well as after bi-lateral sagittal split (BSO) and/or Le Fort I osteotomies.
MATERIALS & METHODS

Patients
This prospective study was conducted from December 2006 to July 2009. The source population consisted of patients who were treated at the departments of Oral and Maxillofacial Surgery (OMFS) of the:
1. University Medical Centre Groningen (UMCG)
2. Rijnstate Hospital Arnhem (RHA)
3. Amphia Hospital Breda (AHB)
4. Medical Centre Leeuwarden (MCL).

Patients meeting the inclusion criteria were eligible for this study (Figure 1). All patients were informed regarding the treatment options prior to surgery and were required to provide informed consent in order to participate in the study. The surgeons recruited the participants and subsequently assigned them randomly to two treatment groups a day before (in case of osteotomies) or immediately prior to (in case of fractures) the operation. A statistician generated the randomization sequences using a computerized randomization program. The randomization sequences were linked to a central telephone, which was available 24-hours a day to conceal the sequence until the interventions were assigned. Stratification to hospital was executed in order to detect hospital effects. The study was approved by the Medical Ethical Committee (MEC) of the UMCG, and approved for local workability by the MEC’s of the other centres.

Interventions
The patients were assigned to a titanium control-group (KLS Martin, Gebrüder Martin GmbH & Co. Tuttlingen, Germany) or to a biodegradable test-group (Inion CPS, Inion Ltd. Tampere, Finland). Neither prior to nor after surgery, the patients were aware of the system that had been used.

All plates and screws were applied according to the instructions of the manufactures (with prescribed burs and taps). The screw holes were predrilled for both the titanium as for the biodegradable screws, and subsequently pre-tapped for the biodegradable screws. For fixation of mandibular osteotomies and fractures 2.5-mm biodegradable or 2.0-mm titanium plates and screws were used, whereas 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used for fixation of zygoma fractures, Le Fort I fractures, and Le Fort I osteotomies. Each participating OMF surgeon performed 2 ‘test-surgeries’ using the biodegradable system in order to acquire the slightly different application-skills, i.e., pre-tapping the screws and pre-heating the plates, and to get used to the different dimensions. These ‘test-surgeries’ were not included in the study.

Outcome measures
The primary outcome measure was ‘bone healing 8 weeks after surgery’, which was defined as follows:
1. absence of clinical mobility of the bone segments assessed using bi-manual traction on the distal and proximal bone segments;
2. absence of radiographic signs of disturbed bone healing assessed on an orthopantomogram (OPT; all indications), a lateral cephalogram (osteotomies), an occipito-mental-radiograph (zygoma fractures), and a fronto-suboccipital radiograph (mandible fracture).

The following secondary outcome measures were assessed:
1. clinical: occlusion, palpability of plate/screw, wound dehiscence, and signs of inflammation;
2. radiographic: position of the bone segments (position of teeth, path of the mandibular canal, and contour of cortical structures);
3. patient-related (by self-evaluation): pain reported on a Visual Analogue Scale (VAS; ranging 1-100) and mandibular function evaluated by the mandibular function impairment questionnaire (MFIQ (145); ranging 17-85);
4. handling characteristics (plate adaptation, drilling/tapping, screw insertion, and wound closure recorded on a scale of 1-10).
5. cost-effectiveness: direct (hospital, surgeon, and time related) and indirect (discontinuing employment process) costs were reported on a questionnaire.

Figure 1. In- and exclusion criteria

Inclusion criteria:
- patients scheduled for a Le Fort I fracture, and/or a solitary or multiple (maximum 2) mandibular fracture(s), and/or a zygoma fracture;
- patients scheduled for a Le Fort I osteotomy, and/or a Bi-lateral Sagittal Split Osteotomy (BSO);
- patients (also parents or responsible persons if necessary) who signed the informed consent form.

Exclusion criteria:
- patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);
- patients presented with heavily comminuted fractures of the facial skeleton;
- patients who experienced compromised bone healing in the past;
- patients who were pregnant;
- patients who could/would not participate in a 1-year follow-up (reasons);
- patients who would not agree with an at random assignment to one of the treatment groups, or one of the methods or treatment administered in the study;
- patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);
- patients who experienced cleft lip and palate surgery in the past;
- patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);
- patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.
Post-operative interventions, such as wound irrigation with saline, use of antibiotics, abscess incision and drainage, or removal of plate/screws within 8 weeks were reported separately. The primary and the secondary outcome measures were evaluated 8 weeks following surgery by a colleague of the OMF surgeon who performed the surgery.

**Statistical analysis.**
Hypothesis testing was conducted following the principles of non-inferiority analysis. Based on an expected percentage of bone healing of 95% using a titanium system and a maximum acceptable difference of 5% between the two groups with respect to the primary outcome measure, two groups of 109 patients were necessary to demonstrate non-inferiority with a power of 80% on a significance level of 5%. Taking patient loss during the follow-up into account, it was decided to include 115 patients in each group. The Statistical Package of Social Sciences (SPSS, version 16.0) was used to analyze the data. The means and standard deviations of normally distributed variables as well as dichotome variables were calculated and analyzed using the Independent-Samples T-test or the Fischers Exact-test. Skewed variables were either transformed to obtain normally distributed variables, or (if this could not be achieved) analyzed using non-parametric tests. No interim analyses were performed during the study period.

**RESULTS**

Figure 2 represents the flow of 230 randomized patients during the phases of the study regarding the Intention-To-Treat (ITT)-analysis. The inclusion of the different centres (UMCG, RHA, AHB, and MCL) resulted in 103, 78, 44, and 5 patients, respectively. However, because of violating the study protocol, 7 patients had to be excluded from the analysis. Four other patients, who did not complete the follow-up, were considered ‘nonadherent’ to treatment (‘worst case scenario’). This resulted in the analysis of 111 patients in the titanium group and 112 patients in the biodegradable group. Table 1 shows the baseline data of the analyzed patients. Regarding the Per-Protocol (PP)-analysis, the 4

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Analyzed in biodegradable group (n = 117)</th>
<th>Protocol violations (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol violations (n = 2)</td>
<td>- after randomisation it turned out patients have cleft lip and palate (n = 3);</td>
<td></td>
</tr>
<tr>
<td>Protocol violations (n = 2)</td>
<td>- after randomisation it turned out patient had a psychiatric disorder (n = 1);</td>
<td></td>
</tr>
<tr>
<td>Protocol violations (n = 2)</td>
<td>- randomized to the wrong centre (n = 1).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Analyzed in titanium group (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Lost to follow-up 8-weeks (n = 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Analyzed in biodegradable group (n = 112)</th>
</tr>
</thead>
</table>

Table 1. Baseline characteristics in titanium and biodegradable groups

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Titanium (n = 111)</th>
<th>Biodegradable (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n)</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Female (n)</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Age (mean: sd in years)</td>
<td>31:11</td>
<td>30:12</td>
</tr>
<tr>
<td>Age (range in years)</td>
<td>14-60</td>
<td>14-56</td>
</tr>
</tbody>
</table>

Abbreviations:
n = number
sd = standard deviation
above mentioned patients were excluded, because they did not complete the entire study. Additionally, patients were added to the titanium control group when it was decided per-operatively to switch to the titanium system (25 patients). This resulted in a PP-analysis of 135 patients in the titanium group and 84 patients in the biodegradable group.

Inadequate bone healing of 2 patients in the biodegradable group was reported. One patient had a mobile maxilla one day after surgery, who was re-operated using the titanium system. The second patient had a mobile maxilla after 8-weeks, which eventually healed without intervention. Following the ITT-analysis, 5 patients of the biodegradable group (3 patients lost to follow-up and the 2 above-mentioned patients) and 1 patient of the titanium group (lost to follow-up) showed inadequate bone healing, resulting in a non-significant difference. In the PP-analysis 2 patients of the biodegradable group showed inadequate bone healing (table 2). The ITT-analysis showed significant differences with regard to dehiscence of the plate/screws, palpability of the plate/screws, and abscess formation. There were no significant differences with respect to incorrect occlusion and inflammatory reactions.

There was no statistically significant difference between the 2 groups with regard to the position of the bone fragments 8-weeks after surgery, i.e. 1 patient in the titanium group and 6 patients in the biodegradable group.

The self-evaluation of pain revealed VAS scores lower than 10 for both groups, whereas the MFIQ showed nearly equal scores for the mandibular function. The post-operative interventions, wound irrigation with saline, use of antibiotics, abscess incision and drainage, and removal of plate/screws after 8 weeks, did not significantly differ between the both groups. The handling characteristics revealed significant lower scores for the biodegradable system concerning plate adaptation, drilling/tapping, and screw insertion. Wound closure did not reveal a significant difference. The mean operation time did not differ between the 2 groups, despite the variation in handling characteristics. Regarding the cost-effectiveness, the direct costs were 1024 euro in the titanium group and 1311 euro in the biodegradable group, whereas the indirect costs were 2419 and 2481 euro respectively. These differences were not statistically significant. The results are summarized in Table 2.

An ancillary analysis revealed that there was no centre effect with regard to bone healing. Analysis of the various surgeries did not differ significantly between the groups (table 3). In 25 patients who were included in the biodegradable group, the OMF surgeon made the decision to switch to the conventional titanium system per-operatively. The main reasons for switching were handling characteristics and material failure, including plate/screw fracture (n=2), non grip screws (n=8), inadequate position of bone segments after fixation (n=6), dimension of plate and screws (n=1), ‘unfavourable split’ (n=1), and inadequate stability after fixation (n=7). Figure 3 shows the distribution of switches during the study. The ‘unfavourable split’ occurred in a BSO-patient and was considered an adverse event.

### Table II. Outcomes titanium versus biodegradable

<table>
<thead>
<tr>
<th>Description</th>
<th>Titanium group (n)</th>
<th>Biodegradable group (n)</th>
<th>Significance (S/NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome measure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT analysis (inadequate bone healing)</td>
<td>1</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>PP analysis (inadequate bone healing)</td>
<td>0</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Secondary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-correct occlusion</td>
<td>11</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Palpability plate/screw</td>
<td>44</td>
<td>62</td>
<td>S</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>1</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Abscess formation</td>
<td>5</td>
<td>14</td>
<td>S</td>
</tr>
<tr>
<td>Inflammatory reactions</td>
<td>rubor</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>tumor</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>calor</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>dolor (local)</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>functio laesa</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Radiographic assessment</td>
<td>Changed position bone segments</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Self-evaluation of patient</td>
<td>Pain VAS; mean (sd)</td>
<td>6 (13)</td>
<td>8 (13)</td>
</tr>
<tr>
<td></td>
<td>MFIQ; mean (sd)</td>
<td>37 (17)</td>
<td>35 (14)</td>
</tr>
<tr>
<td>Postoperative interventions</td>
<td>Irrigation with saline</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Abscess incision and drainage</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Removal plate/screws after 8 weeks</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Handling characteristics</td>
<td>Plate adaptation (mean;sd)</td>
<td>8.5;0.9</td>
<td>7.3;1.9</td>
</tr>
<tr>
<td></td>
<td>Drilling/tapping (mean;sd)</td>
<td>8.7;1.0</td>
<td>7.1;1.9</td>
</tr>
<tr>
<td></td>
<td>Screw insertion (mean;sd)</td>
<td>8.7;1.1</td>
<td>7.0;2.1</td>
</tr>
<tr>
<td></td>
<td>Wound closure (mean;sd)</td>
<td>8.7;1.0</td>
<td>8.3;1.7</td>
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<tr>
<td>Cost-effectiveness</td>
<td>Direct costs</td>
<td>1024</td>
<td>1311</td>
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<tr>
<td></td>
<td>Indirect costs</td>
<td>2419</td>
<td>2481</td>
</tr>
<tr>
<td></td>
<td>Operation time (h:min)</td>
<td>2:12</td>
<td>2:20</td>
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* Tested one-sided
† Tested two-tailed
S Significant
NS Non Significant
Table III. Numbers of various performed surgeries

<table>
<thead>
<tr>
<th>Operation</th>
<th>Titanium</th>
<th>Biodegradable</th>
<th>Total</th>
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<tbody>
<tr>
<td>BSO</td>
<td>72</td>
<td>70</td>
<td>142</td>
</tr>
<tr>
<td>Le Fort I osteotomy</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Maxillary osteotomy</td>
<td>24</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>Mandibular fracture</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Le Fort I fracture</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zygomatic fracture</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>111</strong></td>
<td><strong>112</strong></td>
<td><strong>223</strong></td>
</tr>
</tbody>
</table>

**DISCUSSION**

Both the ITT- and the PP-analysis revealed that biodegradable plates and screws did not perform inferiorly to titanium plates and screws regarding bone healing after 8 weeks for both maxillofacial fractures and osteotomies. This implies that the biodegradable system can be safely used without IMF for most indications used in this study (see below). Also concerning the majority of the secondary outcome measures the biodegradable system appeared to be not significantly different to the titanium system. In contrast, the handling characteristics showed a remarkable difference, between both systems whereby biodegradable plates and screws were more difficult in use as compared to titanium plates and screws. This is because biodegradable plates and screws are weaker and, more particularly, bulkier in terms of dimensions. The lack of confidence in a still ‘unknown and new’ biodegradable system, handling differences and having a sense of certainty and confidence regarding the conventional titanium system, may have contributed to the relatively high amount of switches. These should certainly be regarded as adverse events.

The primary outcome measure, i.e. bone healing after 8 weeks, was chosen after several studies regarding the mechanical characteristics of biodegradable plates and screws (130;135;146). It has been concluded that these characteristics were less favourable as compared to titanium plates and screws. This may result in insufficient and delayed bone healing percentages. However, titanium plates and screws show high success rates of at least 95% according to the opinions of clinical experts as well as large patient series (32;33;147). Taking these results into account, it is a prerequisite to obtain ‘non inferior’ bone healing when using biodegradable plates and screws. Until now, there is no thorough scientific evidence that biodegradable plates and screws will result in more incomplete or delayed bone healing. It has been reported (144) to use IMF in the first 2 weeks after fixation with biodegradable plates and screws, especially in load bearing situations. In our opinion, this is undesirable.

In the ITT analysis, 7 patients were excluded (figure 2). These 7 patients (1 patient had a psychiatric disorder, 4 had a cleft lip and palate deformity, and 2 were randomized to the wrong centre) did not meet the exclusion criteria. Inclusion of these results would obscure the intended indication whereas exclusion of these results leads to a better applicability and higher accuracy of the results of the study.

The primary outcome measure was not stratified for indication as it could be expected that the bone segments would be healed after 8 weeks independent of the indication. The post-hoc analysis resulted in a non-significant result between the groups. However, the relatively low number of Le Fort I fractures impedes the eloquence of the results of the ITT-analysis for this indication. By contrast, the high number of inclusions of the other indications implies a good eloquence of the results of the ITT-analysis.

The study was performed in 4 hospitals and different surgeons did the operations. This implies good generalizability. On the other hand, several surgeons could imply diminished power of the study as a result of a possible learning curve factor. However, it appeared that...
the switches of the biodegradable to the titanium system took place over the entire study (figure 3). Moreover, the switches were made by all participating surgeons and centres. It can therefore be expected that the performance of the Inion CPS biodegradable system in other hospitals will not be inferior to the conventional titanium system.

In the materials and methods section it is stated that evaluation of outcome measures was planned to be performed by a colleague of the OMF surgeon who performed the surgery. Despite the intended protocol, in too many cases it turned out to be practically unfeasible to perform the evaluation of the outcome measures by a different OMF surgeon than the OMF surgeon who performed the surgery. This phenomenon may have introduced observer bias.

In summary, it is concluded that regarding bone healing after 8 weeks, the performance of the Inion CPS biodegradable system is not inferior compared to the titanium system regarding the treatment of mandibular-, and zygoma fractures as well as for BSO-, and Le Fort I osteotomies. However, despite the ‘non inferior’ primary outcome result, the benefits of using biodegradable systems (less plate removal operations) should be demonstrated during a follow-up of minimally 5 years, especially when the large number of patients for whom it was per-operatively decided to switch from the biodegradable system to the conventional titanium system, are taken into account. The presented results are part of a longer running follow-up study and the one year results will be published in the near future.

ACKNOWLEDGEMENT

The authors thank the Stryker company for their support and the supply of the Inion CPS product.