The nanocrystalline hydroxyapatite paste Ostim® may present a new possibility in the treatment of persistent non-union

N McArthur*, WT Fomuki2, MC Tanner3, FX Huber4

Abstract

Introduction
Despite correctly performed orthopaedic surgery of fractured bones, non-union presents one of the severe complications that occur in the field of traumatology. The aim of this study was to discuss the nanocrystalline hydroxyapatite paste Ostim® as an alternative in the treatment of persistent non-union.

Materials and Methods
Between 2003 and 2009, 10 patients (five male, five female) were diagnosed with a persistent atrophic non-union and subsequently treated by resection of the non-union fracture ends and a bone defect filling with the nanocrystalline hydroxyapatite paste Ostim®.

Results
In all cases, the fractures were primarily treated with an appropriate type of osteosynthesis. Seven cases were treated with plate osteosynthesis, one was treated with an intramedullary nail and two were treated with tension band wiring. The histological and microbiological results obtained from the fracture site did not reveal any form of infection. Full weight-bearing of the treated extremities was allowed on an average of four months after operative treatment of the non-union. Conventional radiographs were used to confirm a complete bone union before full weight-bearing was granted.

Conclusion
The nanocrystalline hydroxyapatite paste Ostim® may offer new possibilities in the treatment of persistent non-union.

Introduction
Despite correctly performed orthopaedic surgery of fractured bones, non-union presents one of the severe complications which occur in the field of traumatology. If further non-operative treatment does not amount to any further bone healing, standard practice calls for surgical debridement, autologous bone grafting and osteosynthetic stabilisation of the fracture site1.2. Furthermore, the treatment must also take the patients’ wishes, comorbidities and fracture localisation into account. Over the last decades, experience in the treatment of non-union has shown that autologous cancellous bone grafts can be used to fill bony defects, which also results in high success rates of bone union3-7. On the other hand, autologous bone harvesting still presents an unacceptable high complication rate at the donor site and may also be very limited in some patients8-12. A new treatment option for bone defect filling following resection of the non-union fracture ends involving the application of nanocrystalline hydroxyapatite has recently become available. Ostim® represents a brand new development among the purely synthetically produced and rapidly absorbable hydroxyapatite compounds. It is mainly characterised by its needle-shaped nanosized hydroxyapatite crystals. Ostim® has recently been successfully used in the fields of oral and maxillofacial surgery and orthopaedic and trauma surgery13-20. The aim of this retrospective study is to summarise the initial results of Ostim® in the treatment of non-infected non-unions.

Materials and Methods
This study conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study. Between 2003 and 2009, 10 patients (five male, five female) were diagnosed with a persistent atrophic non-union and subsequently treated by resection of the non-union fracture ends and a bone defect filling with Ostim®. An absolute contraindication for the use of Ostim® was the diagnosis or even suspicion of a septic non-union. Moreover, we did not use Ostim® in the case of hypertrophic non-union as experience in our department has shown this is normally the result of inadequate stabilisation and thus sufficient re-osteosynthetic surgery alone would normally result in fracture union. General surgical technique—in all cases, the non-union fracture ends were resected to reveal vital bone. Swabs were then taken for histological and microbiological analysis. The

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fracture was then stabilised with an appropriate form of osteosynthesis and the bone defect zone was filled with a maximum of 10 ml of Ostim®. In four cases autologous bone graft was used for supplementary defect filling.

Material properties of the hydroxyapatite compound Ostim®

Ostim® (Fa. Osartis, Obernburg, Germany) is a newly developed, fully synthetic and fully resorbable injectable nanocrystalline paste \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\) and consists of a suspension of pure hydroxyapatite in water prepared by a wet chemical reaction. The needle-shaped hydroxyapatite crystals form agglomerates in transmission electron microscopy (Figure 1). Ostim® paste does not harden after application into the bone and is free of endothermal heating. It is characterised by a large bioactive specific surface area of 106 m² g⁻¹. The atomic ratio of calcium–phosphorus is 1.67².

Results

In our retrospective analysis, 10 patients were identified with an atrophic, aseptic non-union between 2003 and 2009. The age of the patients at surgery ranged from 13 to 78 years (Table 1). In all cases, the fractures were primarily treated with an appropriate type of osteosynthesis. Seven cases were treated with plate osteosynthesis, one was treated with an intramedullary nail and two were treated with tension wires. The histological and microbiological results obtained from the fracture site did not reveal any form of infection. The histological results also revealed that in all 10 cases an atrophic non-union was present. In five cases an implant breakage occurred at the site of the non-union (Figure 2a–h). The mean amount of Ostim® applied at each bone defect was 5ml. In four cases further supplemental autologous bone graft was used. A systemic or local reaction to the bone replacement material Ostim® was not observed. In two cases, an alternate method of osteosynthesis was necessary. Two cases were observed with a prolonged serous wound secretion without any signs of infection. A surgical revision was not necessary and the secretion ceased on the fifth and seventh post-operative days in each case, respectively. Full functional mobilisation of the treated extremities was allowed on average at four months after operative treatment of the non-union. Conventional radiographs were used to confirm a complete bone union before full weight-bearing was granted.

Discussion

The current standard treatment of persistent atrophic non-union involves surgical debridement of the fracture end, autologous bone graft transplantation and stabilisation with a suitable form of osteosynthesis. The success rate of fracture consolidation following autologous bone transplantation

Figure 1: Hydroxyapatite crystals in suspensions.

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Table 1 Summary of patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at operation (years)</th>
<th>Fracture</th>
<th>Ostim® (ml)</th>
<th>Spongiosa-Augmentierung zusätzlich</th>
<th>Primary os- teosynthesis</th>
<th>Implant breakage</th>
<th>Osteosynthesis used at operative revision</th>
<th>Time of full weight-bearing (months)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE</td>
<td>Male</td>
<td>46</td>
<td>Patella</td>
<td>3</td>
<td>Nein</td>
<td>Tension wire</td>
<td>No</td>
<td>Tension wire and screws</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>SP</td>
<td>Male</td>
<td>32</td>
<td>Radiusshaft</td>
<td>5</td>
<td>Nein</td>
<td>Non-angularly stable plate</td>
<td>Yes</td>
<td>Non-angularly stable plate</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Male</td>
<td>26</td>
<td>Pilon tibiale</td>
<td>5</td>
<td>Ja</td>
<td>Angularly stable plate</td>
<td>No</td>
<td>Angularly stable plate and screws</td>
<td>8</td>
<td>Prolonged wound secretion</td>
</tr>
<tr>
<td>HI</td>
<td>Female</td>
<td>71</td>
<td>Olecranon</td>
<td>3</td>
<td>Nein</td>
<td>Tension wire</td>
<td>No</td>
<td>Hook plate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>Female</td>
<td>60</td>
<td>Proximalhumerus</td>
<td>5</td>
<td>Ja</td>
<td>Angularly stable plate</td>
<td>Yes</td>
<td>Angularly stable plate</td>
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<td></td>
</tr>
<tr>
<td>JH</td>
<td>Female</td>
<td>74</td>
<td>Humerus shaft</td>
<td>5</td>
<td>Nein</td>
<td>Intramedullar nail</td>
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<tr>
<td>GM</td>
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<td>Distal femur</td>
<td>10</td>
<td>Ja</td>
<td>Angularly stable plate</td>
<td>No</td>
<td>Angularly stable plate</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>AN</td>
<td>Female</td>
<td>35</td>
<td>Pilon tibiale</td>
<td>5</td>
<td>Ja</td>
<td>Non-angularly stable plate</td>
<td>Yes</td>
<td>Angularly stable plate</td>
<td>5</td>
<td>Prolonged wound secretion</td>
</tr>
<tr>
<td>IW</td>
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<td>13</td>
<td>Supracondylar humerus</td>
<td>3</td>
<td>Nein</td>
<td>NWS Platte</td>
<td>Yes</td>
<td>Non-angularly stable double plate</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>TW</td>
<td>Female</td>
<td>78</td>
<td>Humerus shaft</td>
<td>10</td>
<td>Nein</td>
<td>Angularly stable plate</td>
<td>Yes</td>
<td>Angularly stable plate</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

|          |       |                          |                   |             |                                   |                          |                 |                                          |                                      |                                      |
|          |       |                          |                   |             |                                   |                          |                 |                                          | 47 ±22                               | 5 ±3                                 |

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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
Figure 2: (a–c) This 60-year-old patient suffered an atrophic non-union of the proximal humerus with implant failure (PHILOS-System from Synthes). (d) The intraoperative image shows the implant breakage at the non-union level. (e) The broken plate was completely removed, the non-union ends were resected and a new plate was placed. (f) The intraoperative radiograph shows the defect zone now filled with bone replacement material. (g, h) The radiographs done 66 days after surgical revision of the non-union depict a complete fracture consolidation. The patient was free of any pain.

Research study

has been shown to be high in a number of publications\(^3\)\textsuperscript{–}\(^7\). However, prospective randomised studies have to be still conducted to prove the superiority of autologous bone transplantation over other methods. Extremely high complication rates of up to 38% have also been described at the donor sites. These involve chronic pain, infection and fractures\(^8\)\textsuperscript{–}\(^12\).

Bone allografts offer an abundantly available alternative, which circumvents the potential morbidity of autograft harvest, but carries the potential of disease transmission, immunogenicity and possibly lower union rates\(^10\)\textsuperscript{,}\(^21\). Moreover, the structural, mechanical and resorption properties of allografts are usually much altered by processing, preservation and sterilisation techniques\(^10\),\textsuperscript{,}\(^22\)\textsuperscript{–}\(^24\). Depending on the localisation, there is also the possibility of using vascular pedicle bone grafts especially when trying to fill a long segment of bone defect\(^25\)\textsuperscript{–}\(^27\). The successful use of recombinantly-produced growth factors has also been described in the treatment of non-union\(^2\),\textsuperscript{,}\(^28\),\textsuperscript{,}\(^29\).

Ostim\textsuperscript{®} represents a brand new development among the purely synthetically produced and rapidly absorbable hydroxyapatite compounds, which have been widely and successfully used in the fields of oral and maxillofacial surgery, and orthopaedic and trauma surgery\(^13\),\textsuperscript{,}\(^15\)\textsuperscript{–}\(^17\),\textsuperscript{,}\(^19\),\textsuperscript{,}\(^20\),\textsuperscript{,}\(^30\),\textsuperscript{,}\(^31\).

Ostim\textsuperscript{®} is synthesised by a wet chemical reaction of precipitation...
under permanent pH control using CaO dispersed in water under constant stirring to maintain a suspension state and H3PO4 as starting material.22,33. According to the hypotheses put forward by Constanza and Knnaack, such hydroxyapatite compounds accelerate the bony ingrowth into the critical size defect as they closely mimic the required resorptive and osseointegrative properties of poor crystalline apatitic structure of natural bone.36,37. This, in turn, allows for rapid osteogenesis and angiogenesis to take place, both critical steps for successful bone defect augmentation.38. A further study from Guo et al.39 showed that nanocrystalline hydroxyapatite not only promotes the first stage of cell attachment, adhesion and spreading, but also improves the long-term cell proliferation and differentiation. The increased proliferation rate of PDL cells in the presence of nano-hydroxyapatite paste was mechanistically linked to activation of the epidermal growth factor receptor and its downstream targets ERK1/2 and Akt.39.

This confirms the results obtained in a number of different experimental animal models of other studies. Grigoryan et al.40 described the rapid bone ingrowth at a low complication rate following the treatment of jaw defects with Ostim® in dogs in 2000. Our own animal experiments dealing with the filling of critical size defects with Ostim® in New Zealand white rabbits also resulted in swift and uniform bone ingrowth.39. Laschke41 reported a guided neovascularisation directed towards areas of Ostim® degradation in Syrian golden hamster. Spies et al.41 further confirmed the good biocompatibility, osteoconductivity and bone ingrowth in New Zealand whites, but reported a halt in the Ostim® degradation process six weeks following implantation. Comprehensive clinical experience of using the hydrated hydroxyapatite paste as a void filling exists in the field of maxillofacial surgery. Various stomatology publications describe an accelerated fracture healing and bone density increase at a high degree of tolerance. In 1996, Zuev42 treated 395 patients with jaw defects and periobdental abscesses. The complication rate of the 200 patients in the Ostim® group was 1.5% compared to 3.6% in the group with 195 patients treated with allografts. Bezrakow43 achieved excellent results in 1998 after treating 49 patients with Ostim® following cystectomy of benign cyst tumours of the jaw. The defects in all 49 patients were replaced with fresh bone three months following the defect filling. Gerlach13 filled 44 mandibular cysts with Ostim® and reported complete material resorption with an extremely low complication rate. Strietzel et al.20 performed a lateral alveolar ridge augmentation with Ostim® in 14 patients. Six months later, histological results showed good bone ingrowth of the defect and small amounts of Ostim® remnants. Stübinger et al.44 was also able to demonstrate that new trabecular bone is formed after grafting with the nanocrystalline bone substitute after six months.

**Conclusion**

Our data verifies the importance of the nanocrystalline hydroxypatite as a new option in the treatment of persistent atrophic non-union. We would recommend its use for bone defects with a volume of less than 10 ml, but it could also be used as a supplement to autologous bone graft augmentation. In our opinion, the application of Ostim® should always be combined with some form of stable osteosynthesis, preferably with an angularly stable plate, due to its lack of dimensional stability. Our retrospective study does present limitations with regard to the fact that we have analysed a heterogeneous group of fractures and have made no direct comparison with autologous bone transplantation. Further prospective studies need to be performed in order to assess the significance of Ostim® in the treatment of persistent atrophic non-union.

**Acknowledgements**

Nicholas McArthur designed the study, wrote the majority of the manuscript, analysed data and also collected data. Walters Fomuki collected data and wrote a part of the manuscript. Michael Tanner collected and analysed data. He also reviewed the manuscript. Prof. Huber supervised the entire project, reviewed the manuscript and performed the operations of the patients mentioned in this manuscript.

**References**

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