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A prospective histomorphometric and cephalometric comparison of bovine bone substitute and autogenous bone grafting in Le Fort I osteotomies

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ABSTRACT

Purpose: The aim of the present study was the histomorphometric and cephalometric comparison of autogenous bone grafting of the anterior iliac crest and the application of bovine bone substitute concerning new bone formation and postoperative stability in patients undergoing orthognathic Le Fort I osteotomy.

Patients and methods: Twenty-five patients requiring orthognathic surgery with Le Fort I osteotomy were included in this study. Patients were randomly divided into three groups receiving either autogenous iliac crest *BONE* grafting (*BONE*; n = 8) or xenogenic bovine bone grafting (Bio-Oss[®]) in *INTER* (n = 12) or in *ONLAY* (n = 5) position. Histomorphometric analysis was performed using trephine bone biopsies from the autogenous, respectively xenogenic bone grafting region. Postoperative stability was evaluated using telerradiographies of three different timepoints.

Results: All groups showed comparable mineralized fractions in bone biopsies of 50.2% ($\pm 13.2\%$) *INTER*, 46.48% ($\pm 12.3\%$) *ONLAY* and 57.1% ($\pm 20.6\%$) *BONE* as well as comparable percentage of connective tissue. Patients in the *INTER*-group revealed the lowest relapse rate of 20.5% (*INTER*) compared to 30.3% (*ONLAY*) and 33.0% (*BONE*). All groups underwent comparable maxillary advancement and healing time.

Conclusions: Present results indicate that block shaped bovine bone substitute is a promising alternative to autogenous bone grafting to bridge the Le Fort I osteotomy gap in orthognathic surgery.

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1. Introduction

The Le Fort I osteotomy describes a surgical standard procedure mainly used in orthognathic surgery. Hereby the maxillary segment is separated, repositioned and again fixed using mini plates. This allows a three dimensional correction of the upper jaw in cases of malocclusion, midface hypoplasia or in the management of obstructive sleep apnoea (Buchanan and Hyman, 2013). Large maxillary advancement increases the risk of relapse and pseudarthrosis (Dowling et al., 2005). Therefore, in cases of large

osteotomy gaps (>5 mm) bone grafts are recommended in order to facilitate bony union and enhance long-term skeletal stability (Araujo et al., 1978; Epker and Schendel, 1980). This is based on their biomechanical function as a mechanical barrier preventing relapse and soft tissue herniation as well as biological matrix promoting secondary ossification (Araujo et al., 1978; Epker and Schendel, 1980; Lye et al., 2008). Autogenous bone graft i.e. of the anterior iliac crest is regarded as gold standard (Epker and Schendel, 1980; Kerawala et al., 2001) but is accompanied by donor site morbidity, prolonged surgical time and increased costs. Xenogenic bovine bone mineral (BBM) such as Bio-Oss[®] (Geistlich Pharma AG, Wolhusen, Switzerland) represent an established alternative to autogenous bone graft in the regeneration of small bony defects (Artzi et al., 2001). In CMF based literature, various

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publications deal with indications and properties of BBM (Piattelli et al., 1999; Artzi et al., 2003; Schlegel et al., 2003; Valentini and Abensur, 2003; Hallman and Nordin, 2004; Wildburger et al., 2014). However, less is known about the applicability of bovine bone mineral (i.e. Bio-Oss® block) in the field of orthognathic surgery in particular for bridging large Le Fort I osteotomy gaps.

To our knowledge the current study represents the first prospective comparison of bovine bone substitute (Bio-Oss® block) and autogenous bone graft in bridging large Le Fort I osteotomies. The aim of the present study was the histomorphometric and cephalometric comparison of Bio-Oss® block application and autogenous bone grafting of the anterior iliac crest (gold standard) concerning new bone formation and postoperative stability in patients undergoing orthognathic Le Fort I osteotomy.

2. Material and methods

2.1. Patients

Twenty-five patients requiring orthognathic surgery with Le Fort I osteotomy were included in this study. The sex and age distribution were equal among the groups. All patients had completed skeletal growth and received pre- and postoperative orthodontic treatment. Patients not needing a bone grafting (gap <5 mm) and cleft patients were not taken into account. Patients were randomly divided into three groups. In Group 1 (*BONE*; n = 8) patients received iliac crest autogenous *BONE* grafting, in Group 2 (*BioOss®-INTER*; n = 12) and Group 3 (*BioOss®-ONLAY*; n = 5) patients received xenogenic bovine bone grafting (Bio-Oss® block) either in *INTER*- or in *ONLAY*-position. All patients gave written informed consent to participate. This study was carried out in accordance with the recommendations of the institutional ethics committee (University of Freiburg, Germany) for prospective clinical trials. The presented study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Surgical procedure

All surgical procedures were performed under general anesthesia with single shot antibiotics (Penicillin G 10 Mega, i.v.). Le Fort I osteotomies were preoperatively planned and then operated by the same surgeon according to the standardized procedure (Bell, 1975). Pre-planned final positioning of the maxillary segment was defined by waver and fixed using miniplates and screws (Synthes, Matrix Orthognathic, Umkirch, Germany). Subsequently, in Group 1 (*BONE*) an autogenous bone graft of the anterior iliac crest was obtained and placed into osteotomy gap. Bio-Oss® block was either inserted in *ONLAY* or in *INTER*-position. In the first patients of Bio-Oss® group, *ONLAY*-position was used revealing issues in positioning and fixation of BBM blocks. Clinically the *INTER*-position showed a steadier rest of the block. Therefore, the following patients all received Bio-Oss® block in *INTER*-position. To create data transparency, both groups, *ONLAY* and *INTER* group, were reported and analyzed separately. For *INTER*-position a step had to be prepared with a scalpel in order to enhance primary stability. In both variants Bio-Oss® block was fixed with fibrin glue (Tissuecol®; Baxter-Immuno) and covered with a resorbable bilayer collagen membrane (Bio-Gide®; Geistlich Pharma AG, Wolhusen, Switzerland) (Fig. 1).

After surgery, all patients remained in intermaxillary fixation with elastic bands for 7 days. Patients underwent periodic follow up at regular intervals as per departmental protocol. After a healing period of at least six months (average 11.6 ± 5.7 months), prophylactically all osteosynthesis material was removed under general anesthesia. Simultaneously, cylindrical bone biopsies from the

autogenous, respectively allogenic bone grafting region were taken with a trephine burr (Gebr. Brasseler GmbH & Co. KG) under 600 rpm and constant cooling.

2.3. Histomorphometric evaluation

Bone biopsies were fixed in 4% formalin, rinsed with water, and dehydrated in serial steps of alcohol (70%, 80%, 90%, and 100%), remaining for 3 days in each concentration. Then, samples were defatted for one day with Xylene (Merck, Darmstadt, Germany). Polymerization was accomplished by infiltration with Methylmetacrylat (MMA, Merck), Dibuthylphthalat (Fluka, Steinheim, Germany) and dyed Benzoylperoxid (Merck) for several weeks. Fixed samples were cut into sections of 500 µm and placed on acrylic slides (Martin, Freiburg, Germany). Reduction to a thickness of 80 µm was performed using a rotating grinding plate (Struers, Ballerup, Denmark). To differentiate between Bio-Oss® particles, pristine and newly formed bone, the samples were stained with Azur II (Merck, Germany) and Pararosanilin (Sigma, Steinheim, Germany). Histomorphometric analysis was conducted with a light microscope (Axiovert 135, Zeiss, Koehn, Germany). Pictures were digitally stored. Histomorphometric analysis was achieved by detection of RGB colors with the computer software AnalySISD Soft Imaging system (Olympus Europa GmbH).

2.4. Cephalometric analysis

In total three teleradiographies were performed in each patient (Planmeca Promax, Vertriebs GmbH, Bielefeld). Standardized teleradiography was performed before surgery for surgery planning (T1), immediately post-surgery as radiographic control (T2) and directly before osteosynthesis material removal (T3). For digital analysis and storage r-win (Computer konkret AG, Falkenstein, Deutschland) and Sidexis 2.2 (Sirona Dental Systems GmbH, Bensheim, Germany) were used. The values for the angles SNA (Sella-Nasion-point A) and NL-NSL (Nasal line – Nasion-sella line) were assessed digitally. In order to evaluate surgical changes (T1 to T2) of maxillary advancement (SNA) and maxillary inclination (NL-NSL) or postoperative stability (T2 to T3) appropriate teleradiographies were compared. Angles were taken as absolute values.

2.5. Statistics

All results were explained with descriptive analysis and expressed as percentage, mean and standard deviation.



Fig. 1. Intraoperative image: Bio-Oss® block in *INTER*-position.

3. Results

In total twenty-five patients (12 male, 14 female) participated in this trial. The average age was 26.1 ± 9.7 years (range 17–55). There were no significant statistical differences between all three groups for age, gender or healing time. Operation and postoperative course in all patients was uneventful. The mean healing time was 11.6 ± 5.7 months. Clinically all patients showed a bony bridged osteotomy gap (Fig. 2). Healing was uneventful, except one patient in the *INTER* group who developed a late abscess and pseudarthrosis. In general anesthesia the maxillary sinus was inspected, and the bone substitute material was removed. Osteosynthesis material was partially loose and was removed also. The osteotomy gap was bridged with autologous pelvic bone.

3.1. Cephalometric analysis

In total, patients in the *INTER* ($3.6^\circ \pm 1.22^\circ$) and *ONLAY*-group ($4.7^\circ \pm 3.47^\circ$) underwent a larger maxillary advancement (SNA; T1 to T2) compared to control group (*BONE* $2.4^\circ \pm 1.15^\circ$). However, despite the larger osteotomy gap, postoperative stability (SNA; T2 to T3) showed comparable results in all three groups (*INTER* $0.73^\circ \pm 0.37^\circ$; *ONLAY* $1.4^\circ \pm 0.96^\circ$; *BONE* $0.78^\circ \pm 0.59^\circ$). This results in a postoperative relapse in the antero-posterior direction of 20.5% (*INTER*), 30.3% (*ONLAY*) and 33.0% (*BONE*), respectively. Concerning the maxillary inclination (NL-NSL), the *ONLAY* positioning showed the weakest protecting effect on postoperative relapse. From all groups *INTER*-position seems to be the most appropriate configuration for postoperative stability (Table 1).

3.2. Histology

Samples from all groups were similar. The biopsies showed newly formed mature lamellar bone interconnecting and integrating Bio-Oss®. New bone and Bio-Oss® formed dense trabecular structures. The tissue was well perfused with no signs of inflammation. NBF appeared dark red and could be easily identified from Bio-Oss® with the Azur II Pararosanilin staining (Fig. 3).



Fig. 2. Representative intraoperative image of Bio-Oss® block group 12 months after surgery. Complete bony integration of the BBM block in the osteotomy gap. Osteosynthesis plates are already removed.

Table 1
Cephalometric analysis.

	SNA [°]		NL-NSL [°]	
	T1 to T2	T2 to T3	T1 to T2	T2 to T3
INTER (n = 12)				
mean	3.58	0.73	2.73	0.93
SD	1.22	0.37	2.14	0.73
ONLAY (n = 5)				
mean	4.70	1.43	2.15	1.08
SD	3.47	0.96	1.03	1.18
BONE (n = 8)				
mean	2.35	0.78	3.55	0.94
SD	1.15	0.59	2.73	0.93

Absolute values of maxillary advancement (SNA), maxillary inclination (NL-NSL) (T1 to T2) and postoperative stability (T2 to T3) in degrees [°]. SNA, Sella-Nasion to A-point; NL, nasal line; NSL, nasion-sella line.

3.3. Histomorphometric analysis

The average healing time was 11.6 ± 5.7 months. Regarding the new bone formation (NBF) results revealed differences in between groups: *INTER* 23.3% (± 14.1), *ONLAY* 14.9% (± 18.2) and *BONE* 48.7 (± 27.8). However, all groups showed comparable complete mineralized fractions - the sum of bovine bone mineral (BBM) and NBF or residual bone and NBF- in bone biopsies of *INTER* 50.2% (± 13.2), *ONLAY* 46.48% (± 12.3) and *BONE* 57.1% (± 20.6) as well as comparable percentage of connective tissue (Table 2).

4. Discussion

Postoperative stability and relapse are still challenging issues in extended maxillary advancement (Dowling et al., 2005). Therefore, in cases of large osteotomy gaps (>5 mm) bone grafts are recommended in order to facilitate bony union and enhance long-term skeletal stability (Araujo et al., 1978; Epker and Schendel, 1980). However, autogenous bone is often accompanied by donor-site morbidity at harvesting site, increased surgical time and cost. In this context, usual morbidities such as hematoma, swelling and pain at the donor-site have to be considered as well as severe morbidities and rare complications such as persisting altered sensation and difficulty walking or even perforation at the harvesting site with the risk of peritonitis. And finally, unsightly scars potentially impair well-being and thereby quality of life especially in female patients. Concerning the cost ratio using bone substitute materials, two main aspects have to be considered: the cost of bone substitute materials and the expected reduction of operating time. Both the cost of materials and especially the cost of the operating theatre do vary a lot in each country. Therefore, a representative calculation of cost ratio is always challenging. In addition, as our intention was to examine the feasibility of bovine bone substitutes in Le Fort I osteotomy gaps, the reduction of operating time was not quantified in this study. Nevertheless, in our opinion the reduction of operating time outweighs the cost of bone substitute materials.

Suitable bone substitutes are desirable in order to reduce morbidity and optimize surgical procedure in cases of large surgical advancement. Required properties for bone graft substitutes are a good biocompatibility and biomechanical stability as well as osteoconductive, osteogenic and osteoinductive properties. For long-term success a favorable environment for invading blood vessels and bone forming cells is needed (Janicki and Schmidmaier, 2011). Several allogenic (Epker et al., 1976; Lye et al., 2008; Kuvat et al., 2009), alloplastic (Bell and Jacobs, 1980; Foitzik and Staus, 2003) and xenogenic (Holmes, 1979; Kent et al., 1986; Wolford et al., 1987; Rosen and Ackerman, 1991; Cottrell and Wolford, 1998; Mehra et al., 2002) materials have already been tested as bone substitutes in orthognathic surgery. A major drawback of

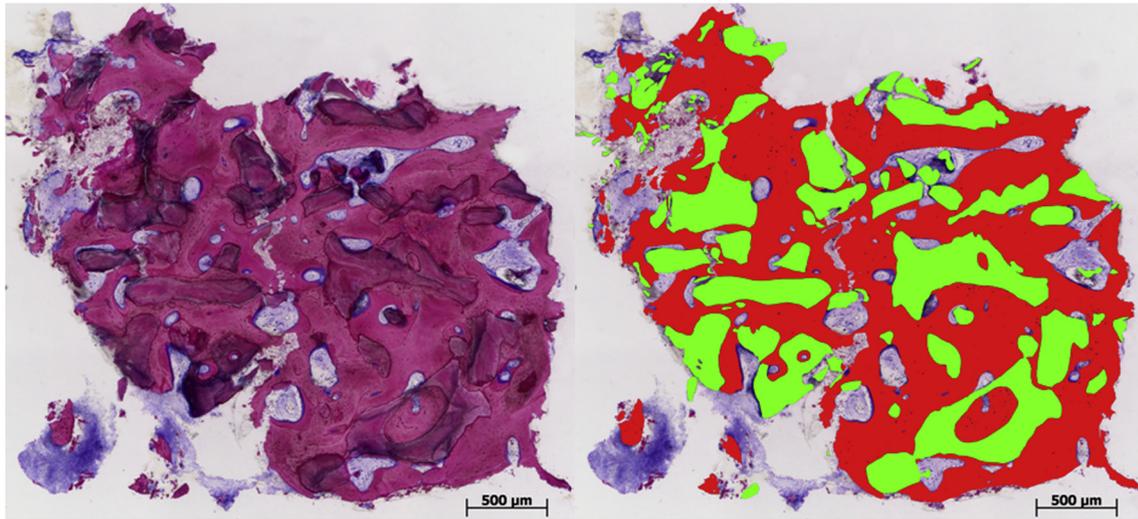


Fig. 3. Representative histological specimen of BioOss[®] group after 12 months. Left: Stained histological specimen with Pararosanilin Azur II. Right: Marked histological Specimen. For the histomorphometric evaluation bovine bone mineral (BBM) was marked green and newly formed bone (NBF) was marked in red color.

alloplastic and xenogenic bone graft materials is the lack of osteoinductivity and the subsequent long healing time (John and Wenz, 2004).

Although already well establish in many fields of oral and maxillofacial surgery (Artzi et al., 2001; Somanathan and Simunek, 2006; Traini et al., 2007), less is known about the applicability of xenogenic bovine bone mineral (BBM) as bone substitute in Le Fort I osteotomy gaps (Rohner et al., 2013; Zanettini et al., 2017). The high porosity and large surface (Weibrich et al., 2000) of BBM (i.e. Bio-Oss[®] block) resembles the physiological bone structure. Furthermore, compared to autogenous bone, the lower resorption of deproteinized bovine bone mineral in the healing period facilitates the penetration of blood vessels and osteoblast through the interconnecting pores of the avital hydroxyapatite trabecular structure (Yildirim et al., 2000; Schlegel et al., 2003; Szabó et al., 2005). The relapse potential in large osteotomy gaps cannot be prevented despite rigid fixation and postoperative elastic intermaxillary fixation. This is attributed to the tendency of the early postoperative resorption of autogenous bone. The volume stability also makes Bio-Oss[®] block a promising candidate as bone substitute in orthognathic surgery because it hopefully will stabilize large osteotomy gaps until complete bony regeneration and thereby preventing horizontal and vertical relapse. Therefore, we hypothesized that due to these favorable properties, Bio-Oss[®] block currently might be the most suitable bone substitute material for bridging osteotomy gaps in Le Fort I osteotomies.

The present histomorphometric and cephalometric results suggest a similar postoperative outcome concerning mineralized fraction (MF) and postoperative stability of either using autogenous

iliac crest bone graft or Bio-Oss[®] block as bovine bone substitute. In our study, complete mineralized fraction which consists of NBF and BBM was 50.2% (*INTER*) and 46.5% (*ONLAY*), respectively. For the *BONE* group, MF (57.1%) consists of residual bone and NBF. Although the MF in all groups was comparable, in the autologous bone NBF (48.7%) was the highest. This was already expected, because most of the transplanted bone underwent remodeling (residual bone 11.9%). Recently, Rohner et al. also applied Bio-Oss[®] in order to promote bony union after Le Fort I osteotomy (Rohner et al., 2013). However, they did not use Bio-Oss[®] block but Bio-Oss[®] collagen. Also, due to the split-mouth design only patients with maxillary advancement less than 5 mm were included. This may explain the lower values for new bone formation (NBF) and mineralized fraction (MF) in our results. Nevertheless, after 6 months, they showed comparable histomorphometric results for the test group (Bio-Oss[®]) concerning new bone formation (39.9%), respectively the amount of Bio-Oss[®] (25.1%) and soft tissue (35.5%) (Rohner et al., 2013). In the group of Rohner et al., because of the small maxillary advancements, the postoperative stability was not evaluated assuming stable relations in osteotomy gaps up to 5 mm. However, in cases of maxillary advancement greater than 5 mm we would recommend the use of Bio-Oss[®] block rather than Bio-Oss[®] collagen. Although collagen is easy to shape, Bio-Oss[®] block offers a primary and biomechanical stability which potentially improves postoperative stability in the early healing period and has less risk of dislocation into the maxillary sinus. The present results suggest that Bio-Oss[®] block in *INTER*-position is the most appropriate configuration concerning postoperative stability. Moreover, after the first surgical experiences, due to aggravated positioning and fixation, we do not recommend *ONLAY*-positioning of BBM blocks.

Comparative studies using porous block hydroxylapatite (PBHA) have shown equal histomorphometric findings. Wardrop and Walford (Wardrop and Walford, 1989) described 11.3%–36.1% bone ingrowth throughout the pores of the implants, whereas Holmes et al. (1988) identified 48.5% HA matrix, 18.0% bone ingrowth and 33.5% soft tissue or vascular space. Due to the larger surface of Bio-Oss[®] block compared to PBHA (Weibrich et al., 2000), we assumed higher new bone formation. Interestingly, this could not be shown in this study. Further research is needed to investigate the correlation between material porosity and new bone formation.

In a representative study, Dowling et al. (2005) observed a mean relapse of 18% of the surgical advancement. Concerning SNA(°) a

Table 2
Histomorphometric analysis.

	% NBF	% Bio-Oss	% Old bone	% MF	% CT	Healing Time
INTER (n = 12)						
mean	23.3	26.9	-	50.2	49.8	11.8
SD	14.1	7.7	-	13.2	13.2	3.7
ONLAY (n = 8)						
mean	14.9	32.4	-	46.5	52.7	14.0
SD	18.2	10.0	-	12.3	14.3	4.6
BONE (n = 5)						
mean	48.7	-	11.9	57.1	42.9	11.3
SD	27.8	-	9.4	20.5	20.5	4.6

NBF = new bone formation; MF = mineralized fraction; CT = connective tissue; Healing Time in months.

20% relapse occurred in a 3 year observation period (Dowling et al., 2005). Hoffman and Brennan (2004) reported a 10% post-surgical relapse in patients with non-bone grafted rigid fixation. Comparability to other studies using porous block hydroxylapatite (Mehra et al., 2002) often is difficult because of different landmarks i.e. incisor tip and mesial cusp of the first molar (Wolford et al., 1987). In addition, Carlotti and Schendel (1987) concluded that orthodontic changes accounted for 75% of the postoperative relapse. Therefore, we preferred skeletal landmarks for our analyses. To our knowledge, this study for the first time compares postoperative stability of bovine bone substitute (i.e. Bio-Oss® block) and autogenous bone grafting in large Le Fort I osteotomy gaps. The present case-control study design offers a direct comparison in the same cohort of patients undergoing surgery under the same conditions. Hereby, the Bio-Oss® group showed comparable (ONLAY 33.3%) of even better (INTER 20.5%) results than control group (BONE 33.0%) concerning postoperative relapse. However, it has to be taken into account, that using 2-dimensional telerradiography narrows the accessibility of complex multi-dimensional postoperative changes. In contrast, 3-dimensional imaging such as Cone Beam CT Scans would have been desirable. 3D analyses allow the evaluation of spatial changes. However, for ethical reasons in the present prospective study design, 3D imaging on three different timepoints was not applicable.

Further studies with greater sample size and longer follow-up are desirable to investigate the long-term result of bovine bone substitute in this specific indication. Also the application in cleft patients who have shown a higher relapse risk after Le Fort I osteotomy (Hochban et al., 1993) could be of interest.

In summary, due to the uncontested osteoconductive, osteogenic and osteoinductive properties, autogenous bone grafting remains the gold standard in bridging of Le Fort I osteotomy gaps. The indication to use bone substitutes in orthognathic surgery (i.e. Bio-Oss® block) has to be made individually, depending on the amount and availability of augmentation as well as the patient's general condition and request.

5. Conclusion

In the present study, for the first time the application of block shaped bovine bone substitute was evaluated in bridging large (>5 mm) Le Fort I osteotomy gaps in orthognathic surgery. The histomorphometric analysis revealed similar mineralized fractions in the Bio-Oss® group and BONE group. INTER-position of Bio-Oss® block additionally promoted postoperative stability. In conclusion, our results indicate that bovine bone substitute can be a promising alternative to autogenous bone graft in orthognathic surgery.

Ethics

The presented study was in accordance with the ethical standards of the ethics committee of the University of Freiburg, Germany and with the Helsinki Declaration of 1975, as revised in 2008.

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Conflicts of interest

All authors have declared no potential conflicts of interest.

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