Clinical Evaluation of a Biphasic Calcium Composite Grafting Material in the Treatment of Human Periodontal Intrabony Defects: A 12-Month Randomized Controlled Clinical Trial

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Background: The aim of this study was to compare the clinical outcome of a novel biphasic calcium composite (BCC) biomaterial versus autogenous bone spongiosa (ABS) or open flap debridement (OFD) for the treatment of intrabony periodontal defects.

Methods: Forty-five subjects with at least one intrabony defect with a probing depth (PD) ≥7 mm and a vertical radiographic bone loss ≥3 mm were enrolled in the study. Subjects were randomly assigned to treatment with BCC (n = 15), ABS (n = 15), or OFD (n = 15). Clinical parameters were recorded at baseline and 12 months after surgery and included the plaque index, gingival index, PD, clinical attachment level (CAL), and gingival recession.

Results: In all treatment groups, significant PD reductions and CAL gains occurred during the study period ($P<0.0001$). At 12 months, patients treated with BCC exhibited a mean PD reduction of 3.6 ± 0.7 mm and a mean CAL gain of 3.0 ± 0.8 mm compared to baseline. Corresponding values for patients treated with ABS were 3.4 ± 0.8 mm and 2.9 ± 0.9 mm, whereas OFD sites produced values of 2.8 ± 0.8 mm and 1.6 ± 0.7 mm. Compared to OFD, the additional CAL gain was significantly greater in patients treated with BCC ($P = 0.002$) and ABS ($P = 0.001$). The additional PD reduction was significant for the BCC group ($P = 0.011$) and borderline significant for the ABS group ($P = 0.059$). There were no significant differences of PD and CAL changes between BCC and ABS groups.

Conclusions: The clinical benefits of BCC were equivalent to ABS and superior to OFD alone. BCC may be an appropriate alternative to conventional graft materials. *J Periodontol 2009;80:1774-1782.*

KEY WORDS

Bone graft; calcium phosphates; clinical trials; debridement; periodontitis; regeneration.

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Periodontal tissue regeneration of intrabony defects has been demonstrated by the use of different therapeutic modalities. These comprise the use of guided tissue regeneration (GTR)[1-3] bone replacement grafts[4-6] and biologic factors, such as enamel matrix proteins[7-9] and growth factors,[10-12] or a combination of these techniques. Although traditional approaches (GTR) use cell occlusive barrier membranes to allow progenitor periodontal ligament (PDL) cells to selectively repopulate root surfaces, the efficacy of bioactive agents is mainly based on mitogenic and chemotactic effects on PDL and alveolar bone cells.[12]

Overall, the use of these techniques resulted in additional benefits in terms of clinical attachment level (CAL) gain and probing depth (PD) reduction compared to open flap debridement (OFD) alone. Nevertheless, the magnitude of CAL and PD changes differed between the studies.[4,5] In particular, the success of GTR is known to be technically sensitive and dependent on various confounders.[13,14] Regarding bone replacement grafts, from a biologic point of view, autogenous bone grafts

doi: 10.1902/jop.2009.090229

have been considered the most predictable or gold-standard material,[15,16] but it is necessary to harvest the graft from a donor area, which might require a second surgical site. Alternatively, xeno- and allografts have been well documented to be suitable as bone replacement grafts.[17-19] However, studies[20-22] frequently state an incomplete resorption of these materials. Moreover, although statistically negligible, there is still a risk of transmitting diseases by the use of allo- and xenografts. The development of synthetic anorganic (alloplastic) materials may offer a useful way to avoid these risks.

Data from controlled clinical trials and meta-analyses demonstrated that the treatment of deep intrabony defects with alloplastic grafts resulted in favorable clinical benefits in terms of CAL gains and PD reductions compared to ODF alone.[4,5] Among these biomaterials, hydroxyapatite,[23-25] bioactive glass,[26,27] calcium sulfate,[28,29] and calcium phosphates[30,31] have been used as bone substitutes. Compared to some of the hydroxyapatites[32] and bioactive glasses,[27] it has been shown that β-tricalcium phosphate and calcium sulfate were resorbable[33-35] and had osteoconductive properties.[36,37]

In the present study, we focused on a novel biphasic calcium composite (BCC)¶ grafting material that consisted of a porous β-tricalcium phosphate and calcium sulfate phase. Due to modified surface activity and ion loading, its osteoconductive behavior might be superior to conventional calcium phosphates. When placed into healthy bleeding bone, the negative-charged surface of this biomaterial accelerated the bone-growth cascade.[38,39] Surface charge is one of the factors that influences the initial (host) response to the implanted graft material, as bone acquires a surface charge when brought into contact with an aqueous environment. The separation in charge between the solid phase of bone and extracellular matrix creates a potential difference between the solid and the liquid called the zeta potential, which influences the type and nature of proteins and cells harnessed by the surface.[40]

Controlled clinical studies on the use of the BCC biomaterial as a bone replacement graft in the treatment of periodontal defects have not been conducted. Therefore, the aim of this clinical trial was to evaluate the clinical outcomes of this novel BCC material in human periodontal intrabony defects compared to autogenous bone spongiosa (ABS) and OFD alone.

MATERIALS AND METHODS

Study Design and Population

The present study was designed as a prospective controlled clinical trial. Three different therapeutic modalities for the treatment of deep intraosseous periodontal defects were compared. Two groups were treated with a regenerative approach: one with the BCC biomaterial and the second with ABS. In the third group, OFD without any bone replacement graft was performed. Forty-five subjects (14 males and 31 females; age range: 33 and 69 years; mean age: 45.4 ± 8.7 years), who were referred for treatment of moderate to severe chronic periodontitis to the Department of Operative Dentistry and Periodontology, University Hospital Aachen, were included in the study. All participants were informed about the risks and benefits of the procedure and signed an informed consent. The study was carried out from June 2006 to November 2008 and was performed according to the Declaration of Helsinki of 1975, as revised in Tokyo in 2004.

The inclusion criteria for patients to participate in the study were: 1) healthy subject between 18 and 70 years; 2) history of generalized advanced periodontitis; 3) presence of at least one deep intrabony defect with PD ≥7 mm and radiographic defect depth ≥3 mm. Patients were excluded in case of: 1) the presence of systemic diseases or medically compromised conditions representing contraindications for periodontal surgery; 2) the use of antibiotics or any drug therapy known to interfere with wound healing during the previous 6 months; 3) a smoking habit; and 4) insufficient dental hygiene characterized by a plaque index[41] (PI) <1. Further, multirooted teeth with furcation involvement were not considered for the study. In these cases, another tooth matching the inclusion criteria was chosen for surgery or the patient was excluded from the study.

Two months before the start of the study, each patient received an initial periodontal treatment including oral hygiene instructions, plaque control, and full-mouth scaling and root planing.

Clinical Measurements

Complete oral and periodontal examinations of each subject were carried out at baseline (prior to the surgical procedure) and 12 months post-surgery. Clinical parameters included PI,[41] gingival index (GI),[41] PD, CAL, and gingival recession (REC). For CAL and REC, the cemento-enamel junction (CEJ) was used as the reference point. In cases where the CEJ was not visible, a restoration margin served as a reference point. All measurements were performed at six sites per tooth using a pressure-sensitive probe# set to a probing force of 0.25 N. Measurements were rounded up to the nearest millimeter. Pre- and postoperative non-standardized radiographs were taken for diagnostic purposes.

All measurements were recorded by a calibrated examiner (UH) who was not aware of the surgical

¶ Fortoss Vital, Biocomposites, Keele, U.K.
# Hawe Click-Probe, Kerr Hawe, Bioggio, Switzerland.

procedure to be performed. To ensure acceptable intraexaminer reliability, the examiner was calibrated to show >90% agreement within ± 1 mm by duplicate measurements of PD and CAL of 30 randomly selected teeth.

Surgical Procedure

At the time of the surgical procedure, subjects were randomly allocated to one of three experimental groups. All treatments were performed by the same surgeon (JMS). In all groups, defects were accessed using papilla preservation flaps. The simplified papilla preservation flap was used to gain access to the root surface and the marginal alveolar bone in areas where the interproximal space had a mesio-distal width ≤2 mm measured at the level of the interproximal soft tissue.[42] The modified papilla preservation technique[43] was used in areas with a mesio-distal width of the interproximal space >2 mm. Flaps were extended horizontally (mesially and distally) to obtain complete access to the intrabony defect. Vertical incisions were performed, if deemed necessary, for better access and sufficient flap mobility for primary wound closure. Granulation tissues were removed from bony defects, and the exposed root surfaces were scaled and planed with ultrasonic instruments and hand curets. The surgical area was rinsed with sterile saline. At this stage, the following intrasurgical measurements were performed: the distance from the CEJ to the bottom of the defect (CEJ–BD) and the distance from the CEJ to the most coronal extension of the interproximal bone crest (CEJ–BC). The intrabony component (INTRA) of the defects was defined as (CEJ–BD) – (CEJ–BC). Further, the defects were categorized as to the number of surrounding osseous walls.

Afterwards, random assignment to the respective treatment was performed. A sealed envelope, with a card indicating the surgical procedure to be applied, was opened by the surgeon immediately after debridement and defect measurements. In the BCC group, the BCC material was prepared according to the manufacturer's instructions and filled into the defects up to the level of the surrounding bony walls (Figs. 1 and 2). In the ABS group, autogenous spongiosa was harvested from the maxillary retromolar area and, in accordance with the BCC group, filled into the intrabony defects. In the ODF group, no filler was used. Finally, the flaps were coronally advanced to obtain complete coverage of the defect. Care was taken to secure an adequate tension-free interproximal closure. Suturing was conducted using both mattress and single interrupted sutures.

Post-Surgical Infection Control

All subjects were instructed to rinse with 0.2% chlorhexidine gluconate mouthrinse** twice a day until postoperative week 4. No periodontal dressing was placed. Antiphlogistic medication (ibuprofen 400 mg, three times a day) was prescribed and used by subjects if necessary. No antibiotics were used. Sutures were removed after 2 weeks. Subjects were not allowed to brush or floss their teeth in the surgical area for 4 weeks. Within the first 2 months, oral hygiene control and professional supragingival tooth cleaning were conducted every 2 weeks. Thereafter, recall visits for postoperative hygiene were performed monthly. No subgingival instrumentation or periodontal probing was done at any of the postoperative recall visits.

Statistical Analyses

For all treatment groups, primary values of continuous variables were recorded as the mean and standard deviation. In all calculations, the deepest site of the tooth was included. Comparison of age among the groups was done using the independent *t* test. For data of categoric variables (bone-wall characteristics), absolute and relative frequencies were calculated and compared among groups using the χ^2 test. Comparisons of all other variables (PI, GI, PD, CAL, and REC) among the groups were performed using the Wilcoxon test. For differences of these parameters from baseline to 12 months in each treatment group, the Wilcoxon signed-rank test was used. All statistical tests were conducted on a global significance level of $\alpha = 5\%$. Data processing and all statistical analyses were performed using a statistical software package.††

RESULTS

All forty-five patients (n = 15 in each group) completed the study. In all treated sites, primary closure was observed at the completion of the surgical procedure. Healing was uneventful in all treatment groups. Infections or suppuration were not observed in any patient. No statistically significant differences were found among the three treatment groups for any of the subject characteristics at baseline (Table 1). Also, there were no statistical differences between the locations of the defects: 26 defects were treated in the lower jaw, and 19 defects were treated in the upper jaw.

In all three treatment groups the initial depth of the intrabony defects was similar. Likewise, there was no difference in the distribution of 1-, 2-, and 3-wall defects among the cohorts (Table 1).

Hygiene indexes in all groups at baseline and 12 months are presented in Table 2. PI scores remained low from baseline throughout the study period. No statistically significant differences were found among the groups. However, 12 months after surgery, the GI

** Chlorhexamed fluid, GlaxoSmithKline, Buehl, Germany.
†† SPSS 11.0 for Windows, SPSS, Chicago, IL.

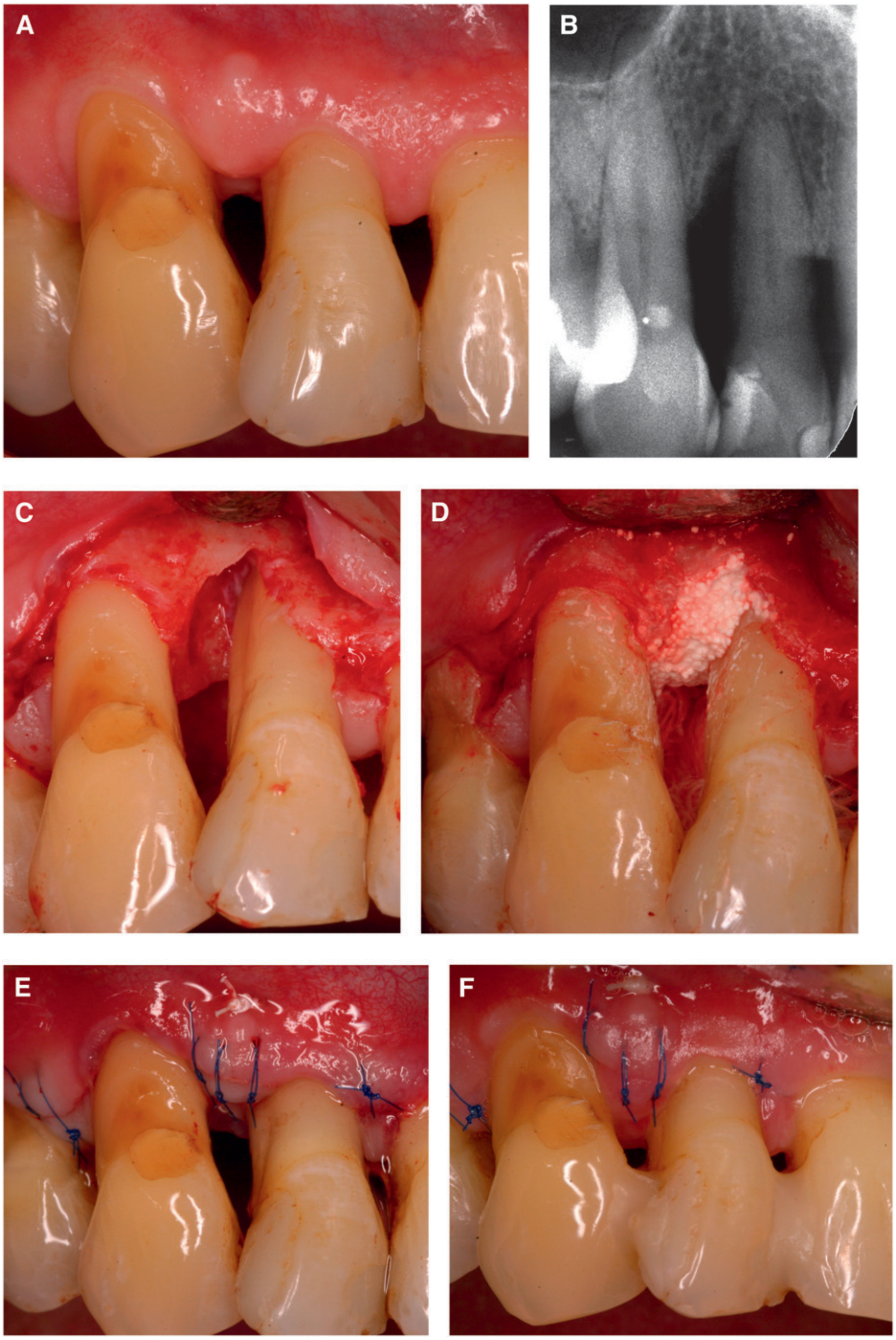

Figure 1.
Treatment of an intrabony defect with BCC on the distal aspect of an upper right second incisor. ***A)*** *Preoperative clinical view.* ***B)*** *Preoperative radiograph showing the corresponding vertical defect.* ***C)*** *Intraoperative view of the debrided 3-wall defect.* ***D)*** *Defect filled with the BCC biomaterial.* ***E)*** *Sutures immediately after flap closure.* ***F)*** *Surgical site 1 week postoperative.*

scores improved significantly in all groups. The postoperative score of GI in the BCC group was significantly increased compared to the final value in the ABS group. All other comparisons of GI among groups did not show significant deviations.

All clinical parameter changes are summarized in Table 3. There were no significant differences in the initial PD, CAL, and REC measurements within the BCC, ABS, and OFD groups. Compared to baseline data, all cohorts exhibited a significant reduction of PD values and CAL gain 12 months after surgery (P <0.0001). The groups treated with BCC and ABS produced a significantly higher gain of CAL than patients treated with OFD alone. Compared to OFD, the additional CAL gain was 1.4 ± 0.8 mm in the BCC group and 1.2 ± 0.8 mm in the ABS group. The difference of CAL changes between BCC and ABS groups was not statistically significant.

Regarding changes of PDs compared to OFD, the BCC group yielded a significantly greater change of PD values (additional PD reduction: 0.8 ± 0.8 mm; P = 0.0108), whereas the additional PD reduction in the ABS group was only borderline significant (0.6 ± 0.8 mm; P = 0.0588). The difference of PD changes between BCC and ABS groups was not statistically significant.

REC significantly increased in all three groups 12 months after surgery. Although the change of REC values was similar in the BCC group (0.5 ± 0.6 mm) and patients treated with ABS (0.6 ± 0.6 mm), it was higher in patients treated with OFD alone (1.2 ± 0.6 mm).

DISCUSSION

Autogenous bone grafts have been considered to be the gold standard among bone replacement grafts because they are osteoconductive and retain cell viability, including osteoblasts and osteoprogenitor stem cells, which facilitate osteogenesis.[44-46] The use of autografts in intrabony periodontal defects has been reported to result in an increased reduction of PD and CAL values compared to OFD alone.[4,5] However, because a surgical donor site is needed and the availability of grafted bone is limited, bone replacement grafts are used because they match the biologic function of autogenous bone grafts and have comparable clinical benefits without the need for a second surgical site. Therefore, and in contrast to most studies,[8,9,23-28] we tested the clinical effectiveness of a novel synthetic biphasic bone graft in the treatment of intrabony defects in comparison to OFD and the use of ABS.

To limit patient- and defect-based factors which might confound the outcome of periodontal surgery, the study was only conducted in non-smokers, in compliant patients with good oral hygiene (PI <1), and with comparable subject and defect characteristics among cohorts (Table 1). Furthermore, during the study period, changes of PI did not differ among groups. Only for the GI were the 12-month values significantly lower in the BCC group compared to the ABS and OFD groups. Nonetheless, this observation should not be interpreted as a relevant bias because the difference between the baseline and 12-month values was similar in all groups (Table 2). The depth of intrabony defects had to be ≥3 mm because the regenerative potential is known to be low in shallow intrabony defects,[13,47] which would impair the comparability of the groups.

All study groups had significant changes of PD and CAL values 12 months after surgery. However, the application of the BCC biomaterial provided significantly greater PD reductions and CAL gains than OFD alone. Similarly, subjects treated with ABS yielded significantly higher CAL gains and a borderline significant increase in PD reductions compared to the OFD group. Compared to the OFD group, the additional gain of CAL and reduction of PD due to the application of BCC in subjects was not significantly different from

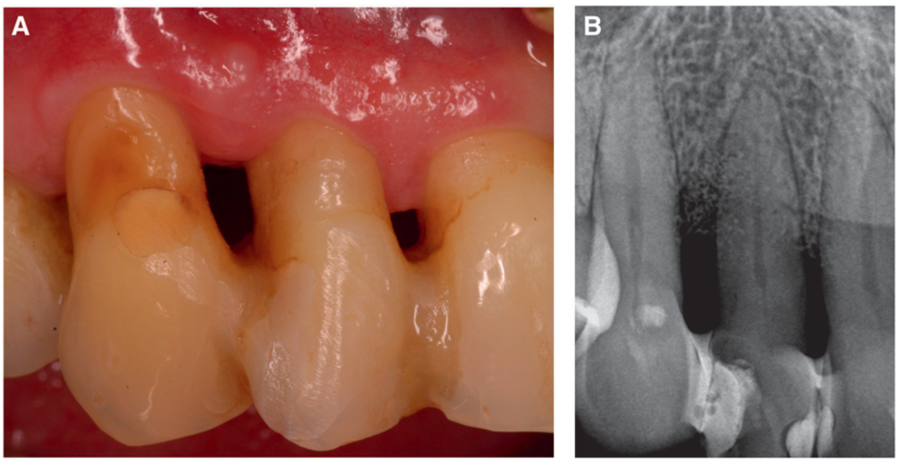

Figure 2.
Example of site in Figure 1: reevaluation 12 months after treatment with the BCC material. ***A)*** *Clinical view of healing result.* ***B)*** *Corresponding radiograph.*

Table 1.

Baseline Subject and Periodontal Defect Characteristics

Variable	BCC (n = 15)	ABS (n = 15)	OFD (n = 15)	*P* Value		
				BCC Versus OFD	BCC Versus ABS	ABS Versus OFD
Age (years; mean [SD])	46.3 (7.1)	45.0 (8.6)	45.0 (10.5)	0.7895	0.7895	1.0000
PI (mean [SD])	0.7 (0.3)	0.6 (0.3)	0.7 (0.2)	0.4003	0.8497	0.3563
GI (mean [SD])	0.7 (0.3)	0.9 (0.2)	0.8 (0.2)	0.7848	0.1210	0.0559
PD (mm; mean [SD])	7.3 (0.7)	7.2 (0.9)	7.1 (0.8)	0.4428	0.6649	0.7569
CAL (mm; mean [SD])	8.1 (0.9)	8.4 (1.7)	7.7 (0.9)	0.2053	0.8965	0.2176
REC (mm; mean [SD])	0.8 (0.9)	1.2 (1.6)	0.6 (0.5)	0.8008	0.6267	0.4270
CEJ–BD (mm; mean [SD])	8.3 (1.2)	8.5 (1.6)	7.7 (0.8)	0.1890	1.0000	0.2213
CEJ–BC (mm; mean [SD])	3.7 (1.2)	3.8 (1.9)	3.4 (0.6)	0.4576	0.7979	0.8286
INTRA (mm; mean [SD])	4.6 (0.7)	4.6 (0.6)	4.3 (0.6)	0.4304	0.9083	0.3284
1-wall (n; [%])	1 (6.7)	2 (13.3)	2 (13.3)	0.5428	0.5428	1.0000
2-wall (n; [%])	8 (53.3)	7 (46.7)	8 (53.3)	1.0000	0.7150	0.7150
3-wall (n; [%])	6 (40.0)	6 (40.0)	5 (33.3)	0.7048	1.0000	0.7048

Table 2.

PI and GI Scores (mean [SD]) at Baseline and the 12-Month Evaluation

Variable	Baseline	12 Months	Difference	*P* Value
PI				
BCC	0.7 (0.3)	0.6 (0.3)	–0.1 (0.3)	0.2520
ABS	0.6 (0.3)	0.5 (0.2)	–0.1 (0.3)	0.2520
OFD	0.7 (0.2)	0.7 (0.2)	0.0 (0.2)	0.3962
P value (BCC versus OFD)	0.7212	0.1308	0.8155	–
P value (BCC versus ABS)	0.5985	0.5579	0.5548	–
P value (ABS versus OFD)	0.4388	0.0925	0.2579	–
GI				
BCC	0.7 (0.3)	0.3 (0.1)	–0.4 (0.3)	<0.0001
ABS	0.9 (0.2)	0.5 (0.2)	–0.4 (0.2)	<0.0001
OFD	0.8 (0.2)	0.5 (0.2)	–0.3 (0.2)	0.0005
P value (BCC versus OFD)	0.7848	0.0203	0.1417	–
P value (BCC versus ABS)	0.1210	0.0083	0.8661	–
P value (ABS versus OFD)	0.0559	0.9832	0.2378	–

– = not applicable.

those treated with ABS. Accordingly, the treatment with either BCC or ABS resulted in nearly the same increase of RECs, which was lower than in the control group treated with OFD alone. The additional CAL gain in the BCC group compared to the OFD group was 1.4 ± 0.8 mm, which corresponds well with the findings of several studies[24-26,28] on alloplastic bone-replacement materials. It is also in accordance with the results of a meta-analysis, in which the additional CAL gain for alloplastic materials ranged from 1.0 mm for bioactive glass to 1.4 mm for hydroxyapatites.[4]

On the other hand, there are a few studies[27,48,49] that did not show a clinical benefit of synthetic graft materials compared to OFD. There might be several reasons for the discrepancies in the clinical outcomes. First, differences in defect characteristics and the surgical methods used might lead to different results. In the present study, papilla preservation techniques, which are known to improve primary closure and postoperative healing results in regenerative procedures, were applied in all treated sites. In the cited studies,[27,48,49] this approach has not been considered. Second, the overfilling of the defects with the biomaterial, as reported by Shirakata et al.[49] may impair primary wound closure and cause different results. Further, contrary to other studies,[9,29,45,49] the high frequency of maintenance and the level of plaque control in our study population, which are known to correlate with beneficial results in periodontal surgery,[2] may have additionally supported postoperative healing.

After all, the surface characteristics of the new BCC material might promote an optimal integration of the graft material with a favorable healing outcome. In contrast to conventional β-tricalcium phosphates, manufacturing and application of the BCC material use a proprietary process‡‡ to establish a negative zeta potential. Based on this concept, the surface of the material will be charged negatively in an aqueous environment. A number of studies[38,39,50,51] have shown that a material that has an electronegative surface charge (negative zeta potential) is more accessible for the attachment and proliferation of osteoblasts than surfaces with no or even a positive electric charge. For the BCC, the formation of a negative zeta potential had recently been demonstrated in vivo and in vitro: Cooper and Hunt[52] evaluated the expression of selected osteogenic markers (alkaline phosphatase, osteocalcin, osteopontin, core binding factor alpha-1, and collagen type 1) in vitro by reverse transcription-polymerase chain reaction in a culture of osteoblasts in contact with different calcium phosphate materials with positive and negative zeta potential values. They demonstrated a strong correlation of a negative zeta potential with the expression of several osteogenic markers. Other authors[51] reported the significance of relative zeta potentials of bone and different biomaterials and their influence on protein adsorption. They showed that the adsorption of specific extracellular matrix proteins onto biomaterial surfaces provided sites for an integrin-mediated osteoblast attachment. In the case of BCC with its negatively charged surface, all osteogenic markers were expressed, whereas the conventional pure-phase tricalcium phosphate with a positively charged surface only induced the expression of osteopontin and alkaline phosphatase.

In the present study, the application of the BCC material was well tolerated and led to superior PD and CAL changes compared to OFD. Notwithstanding, it remains unclear to what extent the CAL gains obtained represent the regeneration of periodontal attachment. For both calcium sulfate[35,53] and calcium phosphate,[34,54] favorable osteoconductive properties and resorption dynamics have been reported; e.g., both materials have been completely resorbed and new bone formation was evident. Because the novel BCC biomaterial combines these properties

‡‡ Zeta Potential Control (ZPC), Biocomposites.

Table 3.

Clinical Parameters at Baseline and the 12-Month Evaluation

Variable	Baseline	12 Months	Difference	*P* Value
PD				
BCC	7.3 (0.7)	3.7 (0.7)	−3.6 (0.7)	<0.0001
ABS	7.2 (0.9)	3.8 (0.9)	−3.4 (0.8)	<0.0001
OFD	7.1 (0.8)	4.3 (0.8)	−2.8 (0.8)	<0.0001
P value (BCC versus OFD)	0.4428	0.0670	0.0108	–
P value (BCC versus ABS)	0.6649	0.9821	0.4853	–
P value (ABS versus OFD)	0.7569	0.1155	0.0588	–
CAL				
BCC	8.1 (0.9)	5.1 (0.9)	−3.0 (0.8)	<0.0001
ABS	8.4 (1.7)	5.6 (1.4)	−2.8 (0.9)	<0.0001
OFD	7.7 (0.9)	6.1 (1.2)	−1.6 (0.7)	<0.0001
P value (BCC versus OFD)	0.2053	0.0335	0.0002	–
P value (BCC versus ABS)	0.8965	0.3714	0.4395	–
P value (ABS versus OFD)	0.2176	0.2662	0.0010	–
REC				
BCC	0.8 (0.9)	1.3 (0.8)	+0.5 (0.6)	0.0156
ABS	1.2 (1.6)	1.8 (1.5)	+0.6 (0.6)	0.0078
OFD	0.6 (0.5)	1.8 (0.7)	+1.2 (0.6)	0.0001
P value (BCC versus OFD)	0.8008	0.1111	0.0068	–
P value (BCC versus ABS)	0.6267	0.5110	0.7623	–
P value (ABS versus OFD)	0.4270	0.5692	0.0128	–

– = not applicable.

with the zeta potential-mediated promotion of osteoblast attachment, it can be assumed that this material has the potential to be replaced by new bone, as was shown in a recent report[40] on maxillary sinus augmentation. Although standardized radiographs were not taken in the present study, 12 months after treatment with BCC, radiographic defect fill with bone-like radiopaque tissue, which was indistinguishable from native bone and, therefore, considered new bone, was observed. Nonetheless, the clinical findings of this study must be validated by reentry and/or by histologic analysis in future studies to examine the quality of the defect fill. Moreover, the results of the present study are only applicable to intrabony defects. For other types of defects, no results are available. Finally, it must be emphasized that sample size of this trial is limited. However, to the best of our knowledge, this is the first study to test the clinical feasibility of this BCC material in patients with periodontal intrabony defects. Further studies with a higher number of subjects and long-term observations should verify the findings presented here.

CONCLUSIONS

Within the limits of this randomized clinical trial, the application of a novel BCC grafting material with a modified surface charge for treatment of intrabony defects resulted in a significantly higher reduction of PDs and clinical attachment gain compared to OFD. The beneficial clinical results were comparable to those after application of an autogenous graft, indicating that the BCC material is a suitable bone replacement material for intrabony defects.

ACKNOWLEDGMENTS

The study was supported, in part, by Biocomposites, Keele, United Kingdom. The authors report no conflicts of interest related to this study.

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Submitted April 21, 2009; accepted for publication June 21, 2009.