Injectable Calcium Phosphate Cements for the Reconstruction/Repair of Oral and Cranio-maxillofacial Bone Defects: Clinical Outcome and Perspectives

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Contents

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Abstract

In this chapter, the clinical performance of commercially available calcium phosphate cements (CPCs) used for reconstruction/repair of hard tissues in the oral and cranio-maxillofacial region is reviewed. Literature were collected from the electronic database of PubMed, Web of Science, and Springer Link, respectively, with various combinations of searching strategy of keywords; human preclinical/clinical studies ranging from case reports to randomized clinical trials were enrolled from the period between 1990 and 2016, highlighting the outcomes, complications, contraindications, and cautions related to the use of CPC in craniofacial reconstruction/repair. We conclude that injectable CPCs can be considered as favorable alloplasts for the reconstruction/repair of craniofacial area, when used with sufficient caution and be strict to specific clinical indications.

1 Introduction

The oral and cranio-maxillofacial region of the human being contains several organs including the brain, eyes, ears, nose, and mouth, which are united into a highly complex structure. In addition to the essential biological functions of these organs, the esthetic appearance of the face is considered increasingly important in modern society. Generally, function and form of the underlying skeleton are crucial for proper functioning of organs and attractive facial appearance. Consequently, treatment of injury and diseases or the desire for cosmetic change usually requires (re) arrangement of the underlying bony tissues.

This (re)arrangement of bony structures in the oral and cranio-maxillofacial region remains a clinical challenge for surgeons. In addition to the demanding requirements related to surgical skills and experience of surgeons, the availability of host-friendly and biologically effective synthetic bone grafts called bone substitutes is still limited despite several decades of research. To date, the best-performing bone grafts are still harvested from the patient's own body, which is however associated with drawbacks such as limited availability, increased patient morbidity, traumatic/surgical creation of donor site, and risks for infection. Although this drawback could be overcome by using allografts/xenografts as bone substitute, concerns have been expressed to allografts and xenografts related to their origin (i.e., human and bovine) and the theoretical risk for immune rejection of the graft and for transmission of infectious diseases.

Numerous synthetic bone substitutes have been developed and commercialized to date, but there is no consensus in the literature about an optimal formulation that can replace autogenous bone grafts. Generally, synthetic bone substitutes vary with respect to their chemical composition, physicochemical structure, and application form. Calcium phosphate cements (CPCs) are an emerging class of synthetic bone substitutes which exhibit chemical similarity to the mineral phase in bone and teeth and therefore are highly osteocompatible and easy to handle due to their self-setting properties. Usually CPCs consisted of powder phase (the precursor matrix) and

liquid phase (the harden agent), depending on individual formulations, the powder phase containing one or more solid compounds of calcium and/or phosphate salts, and the liquid phase could be physiological saline solution or aqueous precursor solution. CPCs are prepared on site of surgery by mixing a precursor powder with a liquid phase; the mixing sets off a mild hardening reaction and becomes solid after final setting is finished. The reaction starts from the precipitation of small apatite crystal inside the mixture, finished with the entanglement of newly formed profound crystal network without radical heat release. Prior to the setting of CPC, the material is injectable/moldable which allows surgeons to manipulate with it according to specific clinical requirement/anatomical situation, such as delivering the materials in less invasive way by injection or reshaping the contour of deficit region by sculpture. Although the mechanical properties of harden CPCs are still inferior to bone tissue or highly sintered calcium phosphate ceramics to date, it is superior to hydrogel or putty forms of other inorganic salt compounds on the mechanical aspect; thus, CPCs are highly suitable for specific applications in the oral and cranio-maxillofacial complex, at the non-load-bearing region where mechanical requirements are less stringent. These unique characteristics of CPCs have therefore attracted a lot of attention and have been investigated extensively in numerous in vitro and in vivo studies; however, information on the long-term clinical performance of CPCs is still scarce or inconsistent so far. Consequently, the purpose of this book chapter is to review the clinical outcome of contemporary injectable CPCs developed for the reconstruction of hard tissues in the oral and cranio-maxillofacial region.

2 Etiology of Bone Defects in the Oral and Cranio-maxillofacial Region

Cranio-maxillofacial defects that require bone grafting can be caused by:

- Infectious diseases (osteomyelitis, periodontitis, etc.)
- Malignant or benign tumor surgery
- Ischemic conditions after radiation therapy (osteoradionecrosis)
- Traumatic injury
- Developmental/congenital diseases

Depending on the severity and complexity of the damage, the treatment approach varies from repair to reconstruction, with different requirements related for the bone graft materials to be used. In the following sections, the most common treatments are briefly addressed.

2.1 Repair of Intrabony Defects Caused by Periodontitis

Periodontitis is an infectious disease causing loss of soft and hard tissues surrounding the teeth. Depending on the progress and prognosis of the disease, the infected teeth may lose their support from the surrounding bony tissue. Therefore, repair of

bony defects around infected teeth is an important aspect of the therapy in addition to treatment of the infection. To this end, various bone substitutes can be used to guide bone regeneration (GBR) into the defect area, usually assisted by the use of membranes (Reynolds et al. 2003). Ideally these criteria materials should resist the chewing force transmit by nearby tooth root and facilitate bone regenerate inside the scaffolds within 3 months for bone replacement.

2.2 Preservation of the Alveolar Volume After Tooth Extraction/ Extraction Socket Management

Tooth extraction is the most commonly performed surgical intervention in the field of dentistry to date. Approximately 40–60% of the initial alveolar bone volume is lost 6 months after tooth extraction (Simion et al. 1998). When multiple teeth are extracted in the same area, bone resorption increases even more (Simion et al. 1994). Insufficient alveolar bone volume at an implant site can inhibit placement of dental implants in an optimal position that support the final prosthetic reconstruction. Immediate postextraction implant placement is a well-accepted protocol to minimize bone resorption when little pathology factor presented on the extracted socket site; however, the concept of placement of dental implants soon after removal of a tooth affected by periapical or periodontal pathology is a matter of debate. In fact, frequently, compromised teeth that are indicated for extraction are involved with infectious conditions, which conventionally contraindicate their immediate replacement with endosseous dental implants (Taschieri et al. 2010). In this situation the dilemma that clinicians face is how to manage tooth extractions to provide for the future placement of a dental implant or to maximize ridge dimensions for the fabrication of a fixed or removable prosthesis. Although all alveolar ridge preservation studies demonstrated beneficial results, no one particular grafting material has proven superior to others; the benefit of alveolar ridge grafting materials is inconclusive (Horowitz et al. 2012). Nevertheless, in both maxillary and mandibular regions, biomaterials have been used to maintain as much clinical volume as possible (Kotsakis et al. 2014; Atieh et al. 2015). This can be achieved by, e.g., GBR using particulate autografts, allografts, alloplasts, and/or xenografts with or without the additional support of resorbable or non-resorbable membranes. The bacteria/contamination resist properties of the materials could be emphasized here rather than mechanical strength since the extraction site is open to oral cavity when an advancing mucoperiosteal flap or mucogingiva soft tissue graft was not applied/available.

2.3 Reconstruction of an Atrophic Alveolar Ridge

Bone volume and the corresponding clinical contour change significantly after loss of teeth. Especially in the maxilla, the resulting atrophic alveolar ridge often does not allow for treatment with implants due to a lack of bone volume. To facilitate implant placement, the alveolar ridge often requires bone augmentation both in vertical and horizontal dimensions. At least five methods toward augmentation of the alveolar

ridge can be discerned including (i) guided bone regeneration (GBR), (ii) bone splitting or spreading to expand the ridge, (iii) inlay bone grafts, (iv) onlay bone grafts, and (v) distraction osteogenesis. Several procedures such as GBR and onlay and inlay grafts can be performed using bone substitutes, membranes, or a combination thereof (Felice et al. 2009; Maestre-Ferrin et al. 2009). Distraction osteogenesis is a clinically accepted technique, but the long time needed for distraction and the discomfort of the intraoral distractor are major disadvantages (Saulacic et al. 2009; Ettl et al. 2010). In general, onlay or inlay techniques which require an additional operation at a donor site are more efficient in case of challenging conditions such as vertical augmentation of the alveolar ridge. At the area of the posterior maxilla, placement of implants is particularly complicated. At this anatomical site, bone can be augmented using a specific surgical technique called sinus augmentation (also referred to as sinus lifting or sinus floor elevation).

2.4 Reconstruction of Large Defects Caused by Trauma or Traumatic Therapy

The cranio-maxillofacial complex can be damaged severely by trauma or traumatic therapies such as surgery. In these cases, dentofacial deformity, post-traumatic bone defects, or postoperative contour irregularities are common symptoms. Depending on the complexity of damage, intensive reconstructive procedures are often required to restore oral function and esthetics. In this situation, the substitute materials should fill the defect and fix the broken bony structure rigidly and maintain the contour/volume of missed part of the complex.

2.5 Cosmetic Surgery for Developmental/Congenital Diseases at the Cranio-maxillofacial Region

Genetic deformities such as a cleft lip or palate, hemifacial macrosomia, and hemifacial atrophy are indications for repair and reconstruction of the craniofacial region. In these clinical cases, injectable bone substitutes, which can be applied less invasively, are generally preferred in view of the final prognosis and final cosmetic appearance.

3 Injectable CPCs for Reconstruction/Repair of the Oral and Cranio-maxillofacial Region

Injectable and/or moldable bone substitutes used in cranio-maxillofacial surgery include cements, pastes, putties, and hydrogels. This book chapter focuses on the use of calcium phosphate-based cements.

Calcium phosphate cements (CPCs) can be categorized according to the end product of the setting reaction, i.e., apatite or brushite (bohner 2010). Frequently, carbonate substitutes for hydroxyl groups in apatitic cements, thereby creating

Table 1 Overview of commercialized calcium phosphate cements

Product name	Chemical composition	Mechanical strength			Biodegradable
		Compression strength (MPa)	Young's modulus (MPa)	Tensile strength (MPa)	
BoneSource®	Tetracalcium phosphate (TTCP)/ dicalcium phosphate	6.3–34	3.6–4.7	2	Yes
Calcibon®	62.5% α-tricalcium phosphate/26.8% dicalcium phosphate anhydrous/8.9% calcium carbonate/ 1.8% hydroxyapatite	35–55	2500–3000	4.5	Yes
ChronOS Inject®	73% β-tricalcium phosphate/21% monocalcium phosphate monohydrate/5% magnesium hydrogen phosphate trihydrate	No data	No data	No date	Yes
HydroSet®	Tetracalcium phosphate/dicalcium phosphate/trisodium citrate	14–24	125–240	0.11–0.17	No date
Norian SRS®	α-Tricalcium phosphate/calcium carbonate/ monocalcium phosphate monohydrate	23–55	No data	2.1	Yes

cements with a higher degree of similarity to the mineral phase of the human bone, with which it contains a considerable amount of carbonate ions. Since their invention in the early 1980s, several apatite- and brushite-forming CPCs have been commercialized such as BoneSource®, Calcibon®, ChronOS Inject®, HydroSet®, and Norian SRS® (Van der Stok et al. 2011). The overview of commercialized calcium phosphate cements is summarized in Table 1.

4 Clinical Outcome of CPCs in Reconstruction of the Oral and Cranio-maxillofacial Region

To take a concise overview of the clinical outcome of the use of injectable CPCs for the reconstruction of the oral and cranio-maxillofacial region, literature between 1990 and 2016 were collected from the electronic database of PubMed, Web of Science, and Springer Link, respectively, with different combinations of searching

strategy of keywords, i.e., the keywords of "calcium phosphate cement," "preclinical" or "clinical study," and the anatomic site of cranio-maxillofacial region such as "periodontal," "extraction," "sinus lift," "cranioplasty," "craniofacial," "skull defect," "reconstruction," "repair," etc. were combined, respectively, and an extensive electronic search was performed to identify relevant articles published up to December 2016. After the selection process, studies that met the eligibility criteria were included.

4.1 Reconstruction of Periodontal Intrabony Defects

The first human clinical trial using CPC for periodontal treatment was reported in 1998 by Brown. In this study, a hydroxyapatite cement (HAC), mainly a composition of tetracalcium phosphate and dicalcium phosphate hydrate, was tested inspired by its successful application on the reconstruction and augmentation of nonstress-bearing portion of the craniofacial skeleton. Sixteen patients with moderate to severe periodontal disease and two bilaterally similar vertical bony defects received initial therapy including scaling and root planing followed by treatment with either calcium phosphate cement, flap curettage (F/C), or debridement plus demineralized freeze-dried bone allograft (DFDBA). Standardized radiographs were taken at baseline and 12 months post-surgery for analysis; the extent of the bony defect was determined during initial and 12-month reentry surgery. The clinical attempt of HAC was not promising in comparison to the application of DFDBA: within 6 months of implant placement, 11 of 16 patients treated with calcium phosphate cement exfoliated all or most of the implant through the gingival sulcus. At all 16 test sites, the initially tight visual interface between the radiopaque calcium phosphate cement and the walls of the bony defect gave rise to a narrow radiolucent gap after 1 month post-surgery, meaning the HAC biomaterials were not integrated to the surrounding osseous tissue. This result failed to support the use of HAC for the repair and regeneration of human intrabony periodontal defect; the reason for the failure was not clear, but the authors speculated three possible mechanisms: first is the lack of sufficient flexural stress resistance of set HAC to the normal occlusal forces transmit by nearby natural tooth; the second factor was the lack of sufficient porosity in the hardened HAC to allow bone ingrowth; the innate micropores of set HAC were insufficient to allow for migration and ingrowth of cells, blood vessels, and bone; the third possible mechanism contributing to the clinical failure of HAC was bacterial contamination and colonization of the implant surface and micropores due to the loosen periodontal wound flaps closing (Brown et al. 1998).

In 2008, Shirakata et al. conducted a randomized clinical trial using Norian® cement, a novel formulation of calcium phosphate cement, mainly composed of α-tricalcium phosphate (α-$Ca_3[PO_4]_2$), monocalcium phosphate monohydrate ($Ca[H_2PO_4]_2$ H_2O), and calcium carbonate ($CaCO_3$) mixed with a solution of sodium phosphate (Constantz et al. 1995), as intrabony defect filler of periodontal bone reconstruction. Thirty patients with periodontitis and narrow intrabony defects were enrolled in the study; patients were classified randomly into the CPC graft

group ($N = 15$) or the open flap debridement (OFD) alone group ($N = 15$). After routine basic periodontal treatment, mucoperiosteal full-thickness flaps were reflected, and all granulation tissues were removed completely, and the exposed root surfaces were scaled and planed with hand and ultrasonic instruments. In the graft group, the CPC was filled compactly with injectable CPC from the bottom of the defect close to the residual bone crest. After solidification of the CPC, a periosteal releasing incision was made to allow coronal repositioning of the flap, followed by suturing slightly coronal to the cementum enamel junction (CEJ). The control group was treated similarly, without placement of the CPC. Clinical measurements were performed at baseline and at 3, 6, 9, and 12 months, and radiographs were taken at baseline, 2 weeks, and 6 and 12 months after surgery. The results demonstrated that six cases in the CPC group showed exposure or loss of the graft material during the 12-month treatment, whereas the remaining nine cases (CPC-R group) showed no adverse reaction, including infection or suppuration. Overall, CPC-R and OFD treatment groups exhibited a significant reduction in probing depth and a significant gain in clinical attachment level at 3, 6, 9, and 12 months compared to baseline values. However, there were no significant differences in any of the clinical parameters between the groups. In the CPC-R group, radiographic bone level gain appeared to be greater than in the OFD group. The explanation for the lack of significant differences between CPC-R and OFD groups in any of the clinical parameters might be the fact that most of the defects were narrow three-wall, contained, intrabony defects, in which periodontal healing potentially resulted in complete clinical repair with or without periodontal regenerative therapy (Shirakata et al. 2008).

On the other hand, the setting behavior of CPCs is also crucial for its successful application, as indicated by the positive outcome of a clinical study using a newly developed washout-resistant type of CPC. The material used in the study is named "Chitra calcium phosphate cement" (Chitra-CPC); the powder phase consisted of tetracalcium phosphate (TTCP–$Ca_4(PO_4)_2O$) and dicalcium phosphate dihydrate (DCPD–$CaHPO_4{\cdot}2H_2O$) added with an optimum quantity of gelling agent in dry powder form, the water phase containing disodium hydrogen phosphate (Na_2HPO_4, in 0.2 M concentration) as the setting accelerator (Fernandez et al. 2006). The study included 60 patients and is divided into 3 groups using random number table method. There were two test groups ("CPC group" with calcium phosphate cement and "HAG group" with hydroxyapatite granules), along with a control group (with debridement only). The evaluation was focused on the periodontal soft tissue changes such as reduction in probing pocket depth, gingival recession, and gain in clinical attachment. All parameters in the control and the test groups were evaluated during the 3, 6, 9, and 12 months postoperatively. An overview of the results shows that both the test materials (calcium phosphate cement and hydroxyapatite ceramic granules) are significantly efficacious in healing the periodontal defects when compared with open flap debridement. The calcium phosphate cement formulation (Chitra-CPC) is more efficacious than the hydroxyapatite ceramic granules (Rajesh et al. 2009).

In general, the body of evidence for the use of CPC in periodontology is still limited due the lack of well-designed, randomized clinical trials.

4.2 Extraction Socket Management

Currently, no application of CPCs as sole volume filler at extraction sockets for bone volume preservation was reported. Nevertheless, in case of simultaneous placement of implants after extraction, usually a gap between implant and extraction bone wall will be created due to the mismatch between the shape/dimension of the implant fixture and the socket wall; CPCs are promising candidates to fill the space or to replace buccal bone damaged or lost during extraction, with careful selection on the indicative cases where no pathology factor exists or pathogeny of chronic infection could be eliminated. Taschieri reported a prospective study that evaluates the clinical outcome of implants immediately placed into fresh extraction sockets for the replacement of endodontically treated teeth with signs of vertical root fracture; sixteen partially edentulous patients, with one tooth scheduled for extraction and showing clinical signs and symptoms and/or radiological evidence of vertical root fracture, were included in the study. Sixteen transmucosal implants were installed immediately after extraction and careful debridement. The gap between the implant surface and the socket walls was filled using PD VitalOs Cement, an injectable synthetic bone grafting cement consisting of two calcium phosphate pastes (β-tricalcium phosphate and monocalcium phosphate monohydrate). Implant success and survival and radiographic bone loss were evaluated after 1 year of function. Overall implant success and survival rate was 100% at 1 year. All prostheses were successful and in function, 16 implants could be evaluated radiographically after 1 year of function. Peri-implant bone loss averaged 0.48–0.20 mm. Such value was not affected by implant location, lesion type, or bone quality (Taschieri et al. 2010).

4.3 Augmentation of the Maxillary Sinus

In 2000 Mazor firstly reported case series on the application of BoneSource® (hydroxyapatite cement, component of tetracalcium phosphate/dicalcium phosphate) to stabilize cylindrical hydroxyapatite-coated dental implants placed simultaneously during the augmentation of the maxillary sinus. Twenty-six HA-coated dental implants were inserted in ten grafted sinuses of ten patients with traditional lateral approach sinus floor lift surgeries. The cement was thereby placed at the superior aspect of the sinus. Implants were then fully inserted into the grafted compartment. Second-stage surgery was performed 9 months after implant placement, and core biopsies were performed in-between implant fixtures to verify the texture of graft. Prior to implant exposure, patients were evaluated radiographically. Panoramic and periapical radiographs and CT scans were used to assess the radiographic features of the graft material, the newly formed bone, and their close relation to the implants. Clinical criteria at the time of implant exposure included stability in all directions; crestal bone resorption and any reported pain or discomfort were recorded. None of the cases presented any difficulty in achieving initial stabilization; no clinical complications of the sinuses were evident. At second-stage surgery, there was no clinical evidence of crestal bone loss around the implants. All implants were

clinically osseointegrated. All patients received fixed implant-supported prostheses, and the mean follow-up time was 18 months (ranging from 12 to 24 months). Histologic evaluation showed woven bone well integrated with the graft material with numerous osteocytes directly opposed to the surface. Some of the graft material was still present at the end of the core biopsy, undergoing replacement with bone by creeping substitution after 1 year (Mazor et al. 2000).

However, the clinical study of Sverzut et al. provided controversial results with the same commercialize product but different dental implant placement protocols. BoneSource® was used as filling material for maxillary sinus lifting without simultaneous dental implant insertion. Ten patients were enrolled, and traditional lateral approach sinus floor lift procedures were conducted. After a period ranging from 9 to 16 months of healing, all patients showed a gain in height radiopacity according to the radiographic evaluation and did not have postoperative complications; the secondary surgery aimed in installation of dental implant was conducted, clinical evaluation was taken, and the quantity and quality of bone formation were later verified by taking biopsy of the grafted area in the region adjacent to the axis of the implant to be inserted. However, the authors stated that the cement was friable during instrumentation and installation of the dental implant at second-stage operation. In view of these findings, the authors speculated that it was too risky to place implants due to a lack of sufficient bone formation throughout the biomaterials and decided to abort the placement of implants. The histological analysis revealed that new bone formation was minimal, mainly in direct contact with the surface of the bulk material, indicating that large amounts of cement remained in the sinus floor, possibly due to lack of vascularization inside the CPC; the authors therefore suggested that interconnected porosity should be introduced to the materials to improve the ingrowth of new bone tissue, and the success for simultaneous placement of dental implants and cement in Mazor's study are mainly give credit to the residual bone height of enrolled patient (5 mm in average), which can have provided primary stability of implanted fixtures and mechanical support to the applied CPC (Sverzut et al. 2015).

4.4 Augmentation of the Atrophic Mandible Alveolar Ridge

For this challenging situation, injectable CPC can preferably be applied with the assistance of rigid support from either implant or bone wall/chip to resist the deformed force from mastication movement. Hrefer reported cases using Norian skeletal repair system (SRS), a carbonated calcium phosphate bone cement, to augment the alveolar ridge as a single-stage procedure, with simultaneous placement of implants. Briefly a U-shaped vertical osteotomy was made in the mandible anterior region to split the atrophic alveolar ridge into two segments, and subsequently the CPC is applied as inlay filler between both segments. Thereafter, these segments are firmly fixed by either titanium miniplates or dental implants. In this way, the vertical dimension of the alveolar could be increased up to 5–7 mm (see Fig.1a, b). The prosthodontic procedure started 3 months later. In total 40 implants were inserted for 10 patients, and the follow-up period was 60 months. Overall no

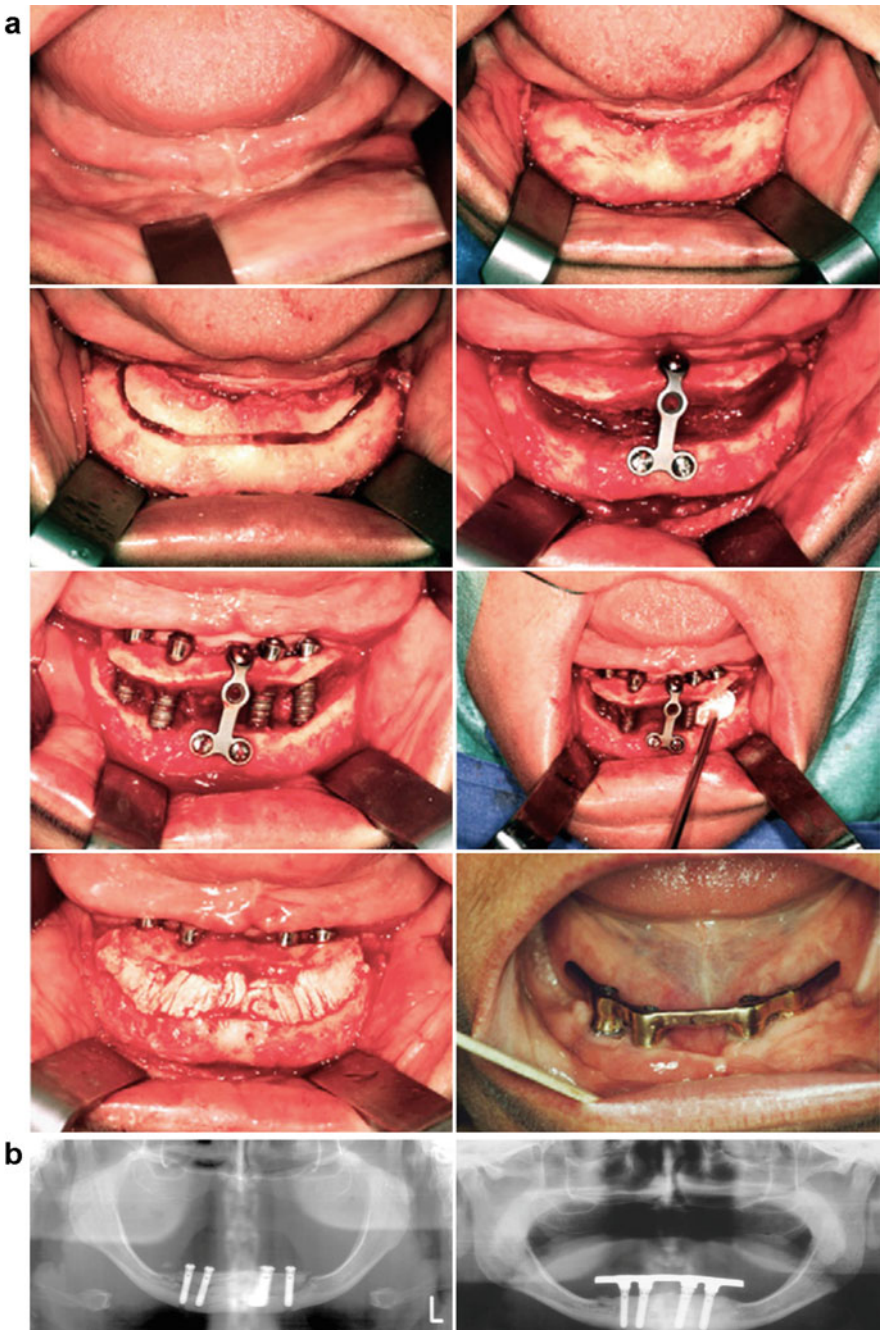

Fig. 1 (**a**) Surgical procedure related to vertical mandible reconstruction. (**b**) Postoperative panoramic examination after augmentation of the atrophic alveolar ridge. (F. Hölzle et al. 2011, reprinted with permission)

fractures or dislocations of implant developed, only one of the implants was lost, and there was one wound dehiscence, but no surgical intervention or revision was necessary. Radiographs showed good consolidation of the bony structure in all cases (Wolff et al. 2004; Hölzle et al. 2011).

In the situation where the initial fixation and subsequent protection of the CPC from this sandwich bone segment technique are not available, attempt using CPC as onlay augmentation on reconstruction of a large mandibular defect has been reported by Stanton. A 10-year-old boy suffered from odontogenic keratocysts (OKC), and a large defect presented in the mandible after giant cyst removed operation including enucleation of the cyst, extraction of all teeth involved in the lesion, and peripheral osteotomy. The remaining bony wall was eggshell thin without perforation. After smoothing and irrigating, Norian bone cement (monocalcium phosphate monohydrate, calcium carbonate, and alpha-tricalcium phosphate powder with a sodium phosphate–buffered solution) was injected to fill the void created from the ascending ramus to the midbody of the mandible, the mucosa subsequently healed, and an uneventful recovery occurred. No recurrence of OKC has been observed 3 years post-surgery. Serial panoramic radiographs have displayed progressive resorption of Norian and replacement with bone. The mandibular height and form have been successfully preserved (see Figs.2a,b and 3a,b) (Stanton et al. 2004).

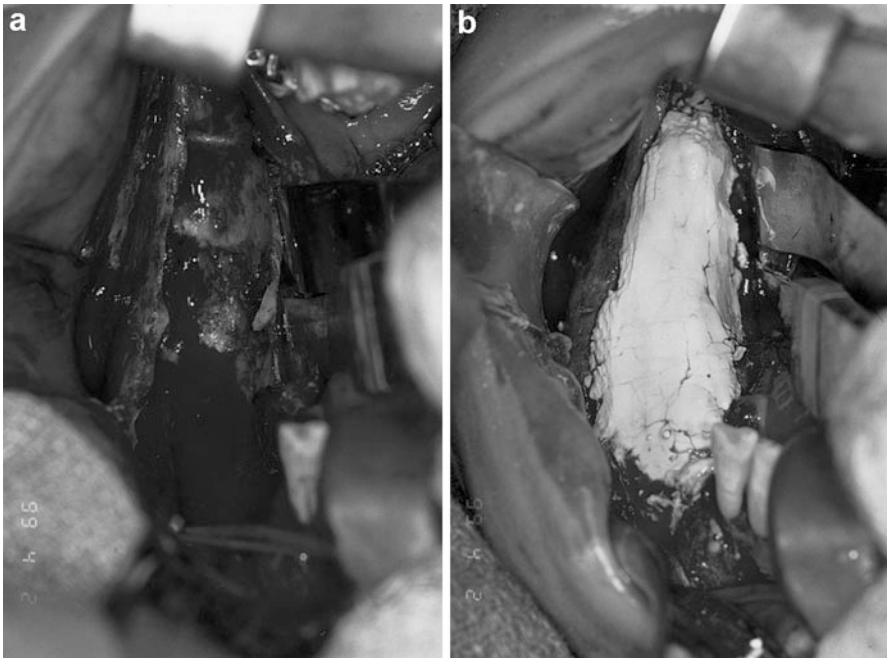

Fig. 2 (**a**) Intraoperative view of inferior border of mandible prior to application of injectable calcium phosphate cement. (**b**) Intraoperative photograph showing injectable calcium phosphate bone cement filling the void created by the lesion. (D.C. Stanton et al. 2004, reprinted with permission)

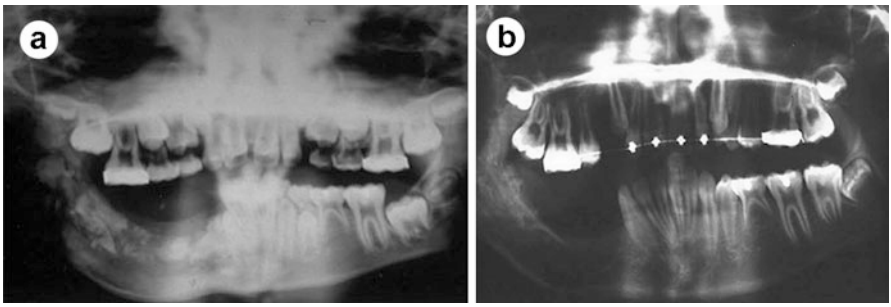

Fig. 3 (**a**) Six-month postoperative panoramic radiograph showing gradual replacement of the graft by bone. (**b**) Three-year postoperative panoramic radiograph showing complete replacement of the graft material by bone, good bone height, and contour with no recurrence of odontogenic keratocyst. (D.C. Stanton et al. 2004, reprinted with permission)

4.5 Reconstruction of the Craniofacial Region

Frequently used commercial CPCs mentioned before such as BoneSource®, Mimex®, Norian®, etc. have been clinically applied in the craniofacial complex for several decades. Successful clinical use of CPCs in this region is restricted to non-load-bearing areas on mature craniofacial skeleton, including reconstruction of full-thickness cranial defects (Mahr et al. 2000), frontal and temporal contouring (Friedman et al. 2000; Chen et al. 2004; Gosain et al. 2009), onlay grafting for augmentation and smoothing contours of skeletal irregularities (Gosain 1997; Jackson and Yavuzer 2000), depressed frontal sinus fracture (Sundaram et al. 2006; Luaces-Rey et al. 2009), nasal augmentation (Okada et al. 2004; Hatoko et al. 2005), or secondary craniofacial contouring (Magee et al. 2004; Van der Stok et al. 2011), with minimal evidence of bone replacement in relatively long-term follow-up of small sample size study design. Typically Gosain reported that cement pastes were used for onlay augmentation to the cranial vault in eight patients, hydroxyapatite (BoneSource®) used in five patients, and calcium phosphate bone cement (Norian® CRS) used in three patients. Patient mean age at implantation was 5.5 years (range, 4–8 years); the mean follow-up term was 5.7 years (range, 1–8 years). All patients had postoperative computed tomographic scans taken 1 year later that demonstrated persistent skeletal augmentation, with a computed tomographic density equivalent to that of the adjacent bone. The only complication in this group was postoperative infection in one patient necessitating partial removal of the implant. The authors concluded that when used for onlay augmentation in the patient where further skeletal growth is negligible (after age 3 in the cranial vault and after age 14 in the facial skeleton), good results could be achieved. Hydroxyapatite cement was also used in a girl with recurrent left-sided forehead recession and frontal bone irregularities. Fronto-orbital advancement at 4 years of age was performed and hydroxyapatite cement paste was applied for augmentation of irregular depressions in the frontal bone with restoration of forehead symmetry and contour. Three yeras later (age 7 years), the patient required a repeat neurosurgical procedure, at which time the

hydroxyapatite onlay was found to be incorporated into the surrounding calvaria but was not been replaced with native bone. Histologic section of a biopsy specimen of the hydroxyapatite onlay demonstrated a rim of bone that had grown around the periphery of the implant, demonstrating good incorporation but no evidence of bone ingrowth within the implant (Gosain et al. 2009).

The promising safety and long-term efficacy of this bone substitute for the repair of craniofacial bone defects in the growing pediatric skull were also reported in 2005. Eight patients who underwent reconstruction of cranial defects using hydroxyapatite cement between the ages of 25 and 100 months (mean, 55 months) were followed up postoperation between 23 and 72 months (mean, 38 months). No mortalities or significant morbidities were encountered in the study population. It has been the authors' experience that hydroxyapatite cement is both biocompatible and resistant to infection when used in sites not contiguous with sinus mucosa and that it is a good alternative to autogenous bone in pediatric craniofacial reconstruction (David et al. 2005).

However, relatively longer-term follow-up and larger sample size studies revealed unfavorable outcome for the use of CPC in cranioplasty compared to the studies mentioned above. Jackson reported a retrospective study of 312 patients who had 449 procedures performed by a single surgeon to reconstruct a calvarial deformity between 1981 and 2001. The main reason for cranioplasty (32.4%) was post-tumor resection deformity, and the main surgical site was the frontal bone (53.2%). Three different materials including autogenous cranial bone, PMMA, and HA cement (BoneSource, Mimex) were used. The median postoperative follow-up was 3.3 years (range, 0.2–10 years). The following variables were assessed to evaluate the outcome: gender, age, indication for surgery, site of cranioplasty, type of material, number of surgeries performed, and complications. The eventual outcome was based on the patient's subjective evaluation of satisfaction during the follow-up period and the occurrence of complications and the need for further surgeries for either revision or improvement. The overall complication rate was 23.6%, in terms of complications and material used; autogenous bone was involved in 20.5% of the complicated cases, PMMA in 29.3%, and HA cement in 32.8%. In the HA cement group, infection and/or extrusion of the material represented 22.4% ($n = 13$ of 58) of the complications. These findings suggested that bone graft and PMMA are still the best materials in calvarial reconstruction. The application of HA cement in craniofacial reconstruction needs to be carefully considered (Moreira-Gonzalez et al. 2003). It seems the infection rate could be higher when CPCs were used for secondary surgery in growing skeleton region at Wong's retrospective chart review. Twenty patients who underwent secondary forehead cranioplasty with hydroxyapatite cement (Norian CRS) were included. Basic demographics including age, sex, and diagnosis were identified, and characteristics of the defects were recorded including size, location, and depth (full vs. partial thickness). The postoperative course was analyzed for length of follow-up and the presence of infections. The result revealed that three patients were lost to follow-up, and all patients had initially acceptable aesthetic results. Of the 17 patients, 10 (59%) ultimately had infectious

complications. Infection occurred on a mean of 17.3 months after surgery (range, 4 month–4 year), and the mean amount of hydroxyapatite used was 32.5 mL (infections) versus 14.3 mL (no infections). Of the ten patients with complications, secondary forehead asymmetry was the most common presentation. Nine patients required surgical debridement and subsequent delayed reconstruction. The use of hydroxyapatite cement in secondary reconstruction has yielded unacceptably high infection rates leading to discontinuation of its use in this patient population. Calcium phosphate cements were thus considered as "off-label" used in the growing craniofacial skeleton (Wong et al. 2011).

Special caution has to be taken since complication rate is very high when CPCs are used for large craniofacial full-thickness defects. Zins summarized 16 patients who underwent correction of large, full-thickness (>25 cm^2) skull defects. The surgical technique included reconstruction of the floor of the defect with rigid fixation to the surrounding native bone, interposition of the cement to ideal contour, and closure of the defect. The mean patient age was 35 years (range, 1–69 years), and the mean defect area was 66.4 cm^2 (range, 30–150 cm^2). Cases were equally divided between BoneSource and Norian CRS. The mean amount of bone cement used was 80 g. Follow-up varied between 1 and 6 years (mean, 3 years). Major complications occurred in 8 of 16 patients, with 1 occurring as late as 6 years postoperatively (Zins et al. 2007). These implanted large amounts of CPC are hardly resorb, which could be confirmed by biopsies taken in another study's reoperations after major complication. Microfragmentation of the cement was often observed inside the recipient site, while the amount of bone replacement was only limited to the peripheral area of the materials. The amount of vascularized bone tissue inside the set CPC was generally very low (Tuncer et al. 2004).

Fragility is another problem for CPC used in large full-thickness cranial defects; to overcome this, there are also attempts to combine CPCs with reinforcements such as tough frames or meshes made by one of the following materials: polylactic acid (PLA) sheets (Cohen et al. 2004), degradable meshes (Greenberg and Schneider 2005), tantalum (Durham et al. 2003), titanium meshes and plates (Van der Stok et al. 2011), etc.

At large area where the CPC was prone to infection due to imperfect closure of soft tissue, or acute adverse events such as seroma and cellulitis formation after surgery, the use of CPC loaded with antibiotic agents, such as cephalothin, was suggested (Matic and Manson 2004; Burstein et al. 2006).

To summarize, the contraindication for the use of CPC in the reconstruction of craniofacial skeleton region, such as infected field, stress-bearing applications, inlay use for reconstruction of large, full-thickness calvarial defects, areas surrounding nonviable bone, abnormal calcium metabolism, metabolic bone disease, immunologic abnormalities, and poor wound healing (Gómez et al. 2005), has to be avoided in all clinical situation. With careful treatment plan in these challenging conditions, injectable CPC can still be considered as favorable bone substitute for the reconstruction of craniofacial area when applied with caution (Gilardino et al. 2009; Afifi et al. 2010).

5 Conclusion and Outlook

Theoretically injectable calcium phosphate cements (CPCs) are highly useful for reconstruction of bone defects in the oral and cranio-maxillofacial region. However, the evidence for successful application of CPC is not unambiguously shown for all clinical indications. Consequently, prospective long-term clinical studies are needed to obtain insight in the long-term behavior of CPC in human patients. These clinical studies have to form the translation basis of further improvements of the material properties of CPCs. In that respect, the strategic priority is firstly to develop CPC that allows for the creation of sufficient mechanical stability at the recipient site – even in non-load-bearing skeletal sites – by optimal formulation of CPC to accelerate setting time of CPC in which more strong washout resistant could be accomplished, which will certainly improve the outcome in many compromised clinical situations. Secondly, development of optimal interconnection porosity inside injectable calcium phosphate cement or optimal degradable CPC formulation which could facilitate vascularization and degradation inside set bulk CPC is also critical for the success of CPC clinical application. And thirdly, introduction of antibiotic effectively aimed at the prevention of pathologic contamination is equally important for successful clinical performance of injectable CPC.

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