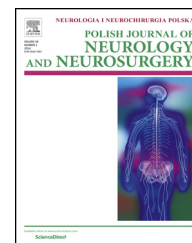


Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

## Original research article

# Reconstruction of large cranial defects with poly-methyl-methacrylate (PMMA) using a rapid prototyping model and a new technique for intraoperative implant modeling



Claudia Unterhofer<sup>a,\*</sup>, Christoph Wipplinger<sup>a</sup>, Michael Verius<sup>b</sup>,  
Wolfgang Recheis<sup>b</sup>, Claudius Thomé<sup>a</sup>, Martin Ortler<sup>a</sup>

<sup>a</sup>Clinical Department of Neurosurgery, Innsbruck Medical University, Innsbruck, Austria

<sup>b</sup>Clinical Department of Radiology, Innsbruck Medical University, Innsbruck, Austria

## ARTICLE INFO

## Article history:

Received 26 November 2016

Accepted 23 February 2017

Available online 10 March 2017

## Keywords:

Cranioplasty

Poly-methyl-methacrylate (PMMA)

Rapid prototyping

Stereolithography

## ABSTRACT

**Background:** Reconstruction of large cranial defects after craniectomy can be accomplished by free-hand poly-methyl-methacrylate (PMMA) or industrially manufactured implants. The free-hand technique often does not achieve satisfactory cosmetic results but is inexpensive. In an attempt to combine the accuracy of specifically manufactured implants with low cost of PMMA. **Methods:** Forty-six consecutive patients with large skull defects after trauma or infection were retrospectively analyzed. The defects were reconstructed using computer-aided design/computer-aided manufacturing (CAD/CAM) techniques. The computer file was imported into a rapid prototyping (RP) machine to produce an acrylonitrile-butadiene-styrene model (ABS) of the patient's bony head. The gas-sterilized model was used as a template for the intraoperative modeling of the PMMA cranioplasty. Thus, not the PMMA implant was generated by CAD/CAM technique but the model of the patients head to easily form a well-fitting implant. Cosmetic outcome was rated on a six-tiered scale by the patients after a minimum follow-up of three months.

**Results:** The mean size of the defect was 74.36 cm<sup>2</sup>. The implants fitted well in all patients. Seven patients had a postoperative complication and underwent reoperation. Mean follow-up period was 41 months (range 2–91 months). Results were excellent in 42, good in three and not satisfactory in one patient. Costs per implant were approximately 550 Euros.

**Conclusion:** PMMA implants fabricated in-house by direct molding using a bio-model of the patients bony head are easily produced, fit properly and are inexpensive compared to cranial implants fabricated with other RP or milling techniques.

© 2017 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

\* Corresponding author at: Clinical Department of Neurosurgery, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. Tel.: +43 512 504 81985; fax: +43 512 504 27453.

E-mail addresses: [claudia.unterhofer@uki.at](mailto:claudia.unterhofer@uki.at) (C. Unterhofer), [christoph.wipplinger@tirol-kliniken.at](mailto:christoph.wipplinger@tirol-kliniken.at) (C. Wipplinger), [michael.verius@tirol-kliniken.at](mailto:michael.verius@tirol-kliniken.at) (M. Verius), [wolfgang.recheis@tirol-kliniken.at](mailto:wolfgang.recheis@tirol-kliniken.at) (W. Recheis), [claudius.thome@tirol-kliniken.at](mailto:claudius.thome@tirol-kliniken.at) (C. Thomé), [martin.ortler@tirol-kliniken.at](mailto:martin.ortler@tirol-kliniken.at) (M. Ortler).

<http://dx.doi.org/10.1016/j.pjnns.2017.02.007>

0028-3843/© 2017 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

## 1. Introduction

The reconstruction of large cranial defects is challenging from a functional, cosmetic and economic point of view. Large defects have been repaired with autologous bone, metal or mesh plates, poly-methyl-methacrylate (PMMA), hydroxyapatite ceramics or carbon fiber reinforced polymer. Each material poses specific advantages and problems [25,31].

Implants made from PMMA are stable, biocompatible, chemically inert, nonconductive, radiolucent, and inexpensive and can be easily placed and modified [12,13,30]. Donor-site morbidity is eliminated and large volumes of non-infectious material are available. Fabricating large implants with PMMA during surgery can be problematic, especially when defects in the frontal or temporobasal area are to be covered [11]. Implant fabrication can be time consuming and implants sometimes appear flat, asymmetrical and cosmetically unacceptable [7,21]. The surrounding tissue is exposed to polymerization heat and to residual monomer [8,16]. PMMA implants are therefore removed during modeling as soon as the resin begins to polymerize and produce heat, although early removal can distort the implant and affect its contour [35]. Techniques developed to circumvent these problems and to separate the fabrication of PMMA implants and the implantation procedure itself include molding of the defect, fabrication of a negative cast from the mold and production of the implant by heat polymerization [7], the duplication of the original bone flap using a molding technique [15,27] or as a template for the direct shaping of metal plates [4].

The availability of helical high-resolution CT scanning and the combination of computer-aided design/computer-aided manufacturing (CAD/CAM) techniques with rapid prototyping (RP) techniques to build 3-D models has simplified the pre-surgical fabrication of accurate, properly contoured implants [16]. RP includes a host of related technologies, all aimed to build objects by adding and binding material in a layering manner [16]. Several materials including PMMA [1,16,21,29,37] carbon-fiber - reinforced polymer [26,36], titanium [4,5,17,33], hydroxyl apatite [10,32] and polypropylene polyester [3,6,19] have been used successfully as cranioplasty materials on the basis of RP-generated (stereolithographic) bio models.

The implementation of these technologies has shortcomings as well, especially when unfamiliar new materials are used for the implant. Design and production of model and implant have to be outsourced [10,26,29,32,36]. This may delay surgery for up to several weeks [26] and is expensive. Customarily only one implant is fabricated and a second one may not be available in case the first one does not fit or becomes damaged during surgery.

We therefore sought a method to simplify the production of cosmetically acceptable large cranial implants. We used RP technology available in-house and an inexpensive material with properties familiar to neurosurgeons and trauma surgeons (PMMA). The goal of this communication is to present the details of our technique and the first results obtained in a consecutive series of patients.

## 2. Clinical material and methods

### 2.1. Patient consent

Informed consent and photo documentation was obtained from all patients.

### 2.2. Study population

N = 46 patients underwent PMMA cranioplasty using the technique described below (Table 1). This was a predominantly adult population (mean age 46 years, and range 7–77 years) with 21 females.

### 2.3. Procedural steps

Axial CT scans were obtained in all patients scheduled for cranioplasty (slice thickness 1.0 mm, kV 140, mAs 120, 512 × 512 matrix, 250 mm FOV, 0° gantry tilt).

CAD/CAM techniques based on the CT data were used to reconstruct a 3-dimensional surface model of the defect including its inner contour and the surrounding calvaria. All reconstructions were performed using either a commercially available software package such as ANALYZE® (Mayo Clinic, Rochester, Minnesota, USA) or Amira® (Konrad Zuse Institute, Berlin, Germany) or the open-source package ImageJ (National Institutes of Health, Bethesda, Maryland, USA) and proprietary programs written in C++.

The model of the defect was constructed by thresholding segmentation and connected component analysis. Details concerning the mathematical algorithms behind the reconstruction of the inner contour (the casting mold) of the defect are published elsewhere [23]. Essentially, two methods were used, depending on location and size. When limited to one hemisphere, it was possible to mirror the unaffected hemisphere to the side of the missing part. The best possible mirror plane was chosen by an experienced software operator after consultation with the neurosurgeon. Once the mirror plane was found, the skull was divided into two pieces and the unaffected hemisphere was mirrored, rotated and translated to the inner surface of the skull defect to obtain the optimal position for a negative casting mold. Mirroring was not possible in cases with the osteoclastic defect crossing the skull's symmetry line (i.e. the midline) in three patients. In these patients CT images of a healthy subject of approximately the same age, race and gender as available in the picture-archiving-and-communication system (PACS) of the hospital were used as a master for the reconstruction. This master was fitted to the individual defect by mathematical methods as such as thin plate spline warping. To reduce central-processing-unit time for time-consuming transformation operations, only relevant parts of the master skull were used first. These parts of the master skull were placed closed to the inner side of the patient's skull to reconstruct the inner surface of the bone implant (Fig. 1).

Once an optimum virtual inner surface of the implant was found, a stereolithographic file (.STL) was generated. The computer file was imported into the rapid prototyping machine (Prodigy Plus®, Stratasys Inc., Eden Prairie, Minn,

**Table 1 – Demographic, clinical and surgical data of all patients.**

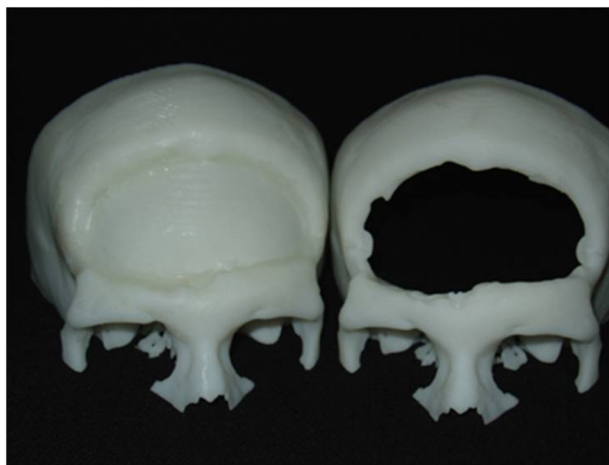
Patient no.	Age (yrs), sex	Cause	Location	Area (cm <sup>2</sup> )	Interval between craniectomy/cranioplasty (mo)	Cosmetic results (grades 1–6)	Complications
1	31, M	Trauma	FTP	57	144	2	None
2	7, M	Trauma	FTP	42	72	1	None
3	20, M	Trauma	FTP	82	9	1	Loosening of fixation system
4	31, M	Gunshot wound	Bifrontal	40	3	1	None
5	49, M	Trauma	FTP	97	24	1	aSDH
6	70, F	Osteomyelitis after craniotomy	T	32	192	2	None
7	74, F	Osteomyelitis after craniotomy	Bifrontal	32	6	1	None
8	59, M	Trauma	FTP	82	36	5	Loosening of fixation system
9	32, M	Osteomyelitis after craniotomy	FTP	79	12	1	None
10	17, M	Trauma	F	20	0.5	1	None
11	45, M	Osteomyelitis after craniotomy	FT	44	2	1	None
12	34, F	Bone deformity after craniotomy	T	72	60	1	None
13	74, F	Trauma	FTP	95	2	2	None
14	66, M	Bone deformity after craniotomy	FT	22	240	1	None
15	69, M	Osteomyelitis after craniotomy	Bifrontal	90	6	1	None
16	59, F	Osteomyelitis after craniotomy	FTP	87.4	6	1	None
17	75, F	Osteomyelitis after craniotomy	FTP	73	6	1	None
18	22, M	Trauma	FTP	113	3	1	None
19	54, M	Bone deformity after craniotomy	FT	38	92	1	None
20	43, M	Osteomyelitis after craniotomy	FTP	113	6	1	None
21	25, M	Osteomyelitis after craniotomy	FTP	117	6	1	None
22	26, M	Tumor and brain edema	FTP	144	9	1	None
23	40, F	Osteomyelitis after craniotomy	FT	23.7	4	1	None
24	77, F	Osteomyelitis after craniotomy	Bifrontal	49.5	12	1	Postoperative empyema
25	50, F	Osteomyelitis after craniotomy	FT	49.2	15	1	aSDH
26	21, F	Trauma	Bifrontal	77.7	17	1	None
27	72, M	Bone deformity after craniotomy	FTP	98.8	88	1	None
28	55, F	Osteomyelitis after craniotomy	FP	58.4	5	1	None
29	26, F	Bone deformity after craniotomy	FTP	90.5	60	1	None
30	52, M	Trauma	F	22.8	7	1	None
31	32, F	Brain edema HELLP Syndrome	FTP	115.2	12	1	None
32	73, F	Bone deformity after craniotomy	FTP	80.1	156	1	EDH
33	20, M	Trauma	FTP	63.4	213	1	None
34	66, M	Osteomyelitis after craniotomy	FTP	64	12	1	None
35	55, M	Osteomyelitis after craniotomy	FTP	112.2	6	1	None
36	42, F	Trauma	FT	64	29	1	None
37	60, M	Osteomyelitis after craniotomy	Bifrontal	59.8	15	1	None
38	69, F	Osteomyelitis after craniotomy	FTP	102.3	36	1	None
39	30, F	Osteomyelitis after craniotomy	FT	37.6	3	1	None
40	76, M	Osteolysis after craniotomy	FTP	119.9	13	1	None
41	33, F	Osteolysis after craniotomy	FTP	110.9	14	1	None
42	45, M	Osteomyelitis after craniotomy	FP	93.1	4	1	None
43	34, F	Osteomyelitis after craniotomy	FT	41.4	24	1	None
44	23, M	Trauma	FTP	93.6	3	1	EDH
45	59, F	Trauma	FTP	100.3	3	1	None
46	46, F	Osteomyelitis after craniotomy	FTP	57.6	3	1	None

Abbreviations and annotations: yrs, years; mo, months; FTP, fronto-temporo-parietal; F, frontal; T, temporal; FT, fronto-temporal; FP, fronto-parietal; PO, parieto-occipital; n.a., not available; aSDH, acute subdural hematoma; EDH, epidural hematoma. Cosmetic results were graded in a 6-tiered scale (grade 1 = excellent; grade 6 = poor result).

USA). The machine utilizes fused deposition modeling (FDM), one of several RP technologies, to produce an anatomical model of the patients head [16,22]. FDM is a non-laser based process that builds the model by depositing layers of thermoplastic material (acrylonitrile butadiene styrene, ABS) one layer at a time [16]. A water-soluble material generates vertical support for all overhanging portions as required

during the modeling process. Once the model is completed, the support material is dissolved using a water-based detergent in a heated ultrasonic bath [16].

The gas-sterilized model was used directly in the operating room as a molding form for the application of PMMA. Before starting the PMMA application, a thin (<0.5 mm) layer of bone wax was applied circumferentially to the border of the



**Fig. 1 – Stereolithographic model of the forehead with the reconstructed inner surface of the implant.**

reconstructed cranial defect to permit easy removal of the implant after hardening and to provide a perfect fit to the patient's cranial defect. Bone wax was also used to fill small irregularities along the defects boundaries. Paraffin oil was used to prevent the PMMA to stick to the stereolithographic model.

After curing *ex vivo*, the implant was separated from the stereolithographic model, trimmed as necessary, rinsed and implanted into the patient using commercial miniplates and screws for fixation as this represented our standard technique.

#### 2.4. Outcome evaluation

Difficulties and complications of the procedure were noted. Outcome was evaluated retrospectively after a minimum follow-up of 3 months in the outpatient clinic. Cosmetic result was evaluated by the patients using school grades, with grade 1 meaning an excellent result, grade 2 a good, grade 3 a satisfactory, grade 4 an adequate, grade 5 a not satisfactory and grade 6 a poor result.

### 3. Results

Results are presented in Table 1 and an illustrative example (Patient No.7) is given in Fig. 2. Forty-six patients underwent PMMA cranioplasty with this method from 2006 to 2013. The mean interval between bone removal and cranioplasty was 8.6 months (range 0–60 months). The majority of defects (in 42 of 46 patients) were by definition large, measuring  $>25\text{ cm}^2$ . The mean size of the defect was  $74.36\text{ cm}^2$  (range 20–144.3  $\text{cm}^2$ ).

Mean operating time was 125 min (range 71–261 min). The surgical procedure was carried out without complications in all patients. No distortion of the PMMA was observed by the untimely manipulation of insufficiently cured material. The intra-operative fit of the implants was good in all patients.

One infection was observed (patient No. 24). Two patients (patient Nos. 5 and 25) underwent surgical evacuation of a post-implantation subdural hematoma and two patients

underwent evacuation of a post-implantation epidural hematoma (patient Nos. 32 and 44) without further sequelae. Two patients underwent minor surgical revision through stab incisions because of loosening of the fixation system. This was evident on postoperative images (on day 4, patient No. 3) or clinically (during the outpatient visit after 1 month, patient No. 8), respectively.

Mean follow-up period was 41 months (range 3 months to 91 months). Forty-two patients exhibited an “excellent” (grade 1) cosmetic result, in three patients the result was “good” (grade 2), in one patient the result was rated “not satisfactory” (grade 5) by the patient himself. This patient had undergone several interventions for cranioplasty at an outside institution. His expectations were deluded by the postoperatively present visibility of the defect covered by a perfectly contoured implant beneath the paper-thin skin and an atrophic temporal muscle. Loosening of one of the cranial fixation devices requiring re-intervention did further aggravate his subjective dissatisfaction with the procedure.

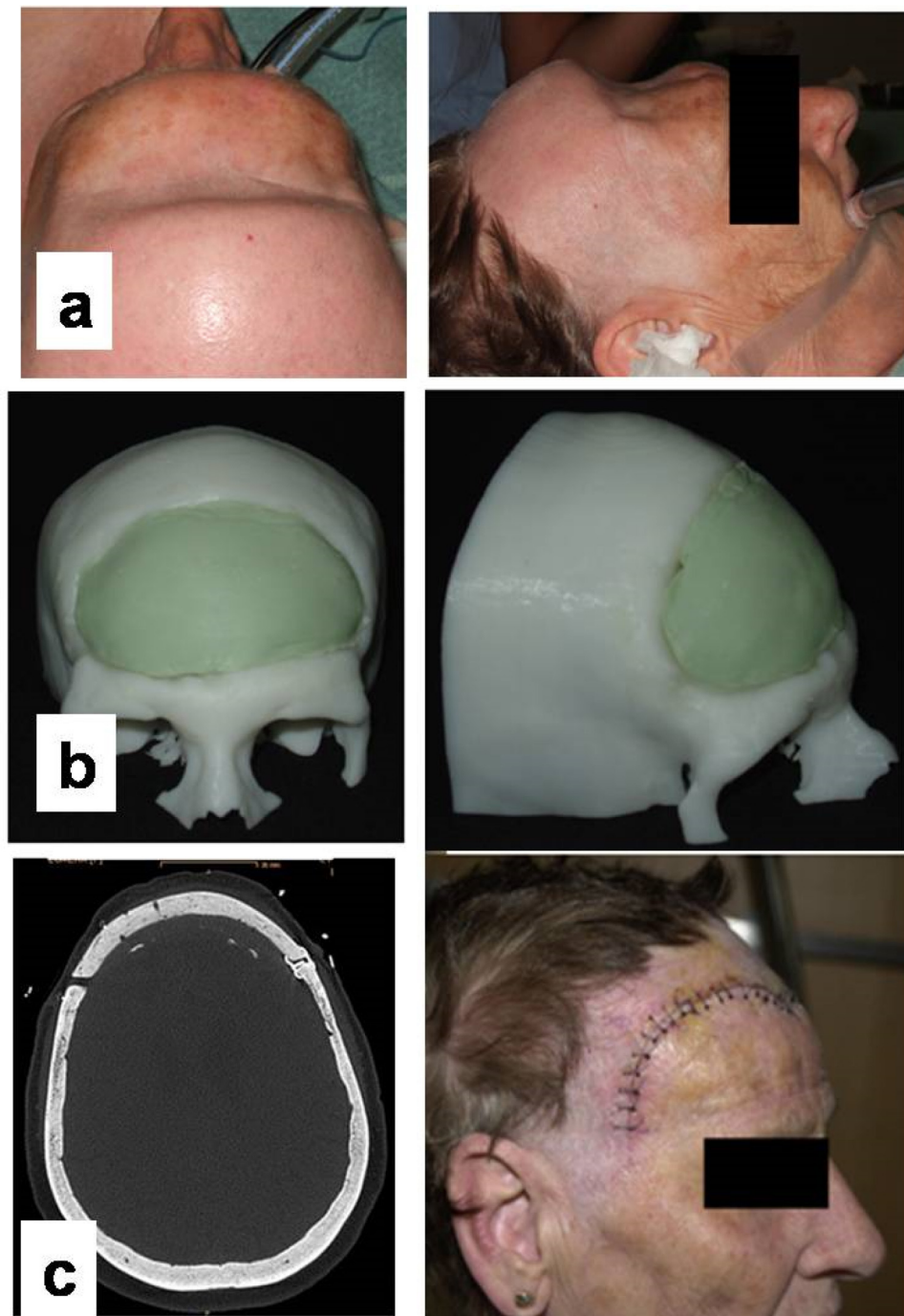
### 4. Discussion

Preliminary results indicate that the technique of methyl-methacrylate (PMMA) cranioplasty described in this paper might be a clinically valuable alternative to other techniques of cranioplasty that use modern rapid prototyping (RP) technologies. The novel aspects presented here are the fabrication of PMMA implants to cover very large calvarial defects and a shortening of the procedure by using technology available in-house and by eliminating two steps during the RP-fabrication of the implant (the creation of a template and the construction of a molding form). This allowed for a reduction of both costs and time without giving in on cosmetic results.

Bone defects that involve the frontobasal and the temporobasal areas are notoriously difficult to reconstruct, especially when the other side of the head is not available for visual inspection during surgery. Our technique provided excellent cosmetic results in  $>91\%$  of the patients. Complications that required re-intervention were observed in seven patients (15%).

Several authors have reported on the combination of stereolithography and acrylic casting for calvarial bone reconstruction using slightly different techniques for implant construction. Agner [1] reported on two patients using a stereolithographic model of the skull defect and a mold technique to produce a methyl-methacrylate implant for cranioplasty. The mold was fabricated using dental grade wax and dental stone. D'Urso [9] described excellent results in 30 patients with defects greater than 4 cm in diameter using stereolithography to produce a craniotomy bio-model and a master implant. This master implant was then used to create an impression cavity mold that was filled with heat-curing PMMA. Major and minor trimming of the implant was necessary in six patients. In one patient, the original master was used also for the production of a second implant. Besides requiring two additional steps, namely the manufacturing of a master implant and the manufacturing of a mold, duplicates of the implant might not be immediately available in case of an imperfect fit or in case of damage during implant trimming





**Fig. 2 – (a) Bifrontal bone defect in patient No. 7 after extirpation of an olfactory groove meningioma and secondary osteomyelitis. (b) Intraoperative implant fabrication using the sterile biomodel of the defect. Note that the biomodel serves as mold for the fabrication of the implant (c). Results 10 days postoperatively.**

when using this technique. Gronet [16] also reconstructed a bio-model of the osteoclastic defect using RP. The lost cranial surface was reproduced by applying a wax pattern to the bone defect in the bio-model. An acrylic implant was fabricated from the wax pattern by creating a gypsum mold and eliminating the wax pattern thereafter. This technique was used successfully in two patients. Yacubian [37] used a molding technique with success in two patients. Solaro [29]

reconstructed the PMMA implant for one patient in the operating room by injection of PMMA into a mold fabricated with CAD/CAM techniques. Finally, Lee [21] also used a mold technique in a subgroup of 17 patients in a study comparing three types of cranioplasty in patients with defects  $>100\text{ cm}^2$ . The use of heat-cured prefabricated PMMA prostheses allowed operation time, blood loss and infection rate to become comparable to patients in whom the own bone was available

for reinsertion. Three patients required reoperation either because of wound infection, or aseptic wound dehiscence, or an epidural hematoma.

Using our technique and PMMA as the implant material, a gas-sterilized bio-model ready for operating room use is available within 48–72 h. To produce the model from the CT data requires up to 8 h of software operator and technician time, typically 45 h for the automated plotting process and additional 5–8 h for the cleaning process in the ultrasonic bath. Plotting time can be reduced further by limiting model fabrication to the bone defect and its immediate surroundings. The intraoperative modeling of the final implant is accomplished within minutes. This compares well with time frames cited by authors using commercially supplied, CAD/CAM-constructed alloplastic cranial implants [10,26,29,32,36].

Material costs for CAD/CAM-designed PMMA implants are low, amounting to 81 Euros for the PMMA and approximately 450 Euros for the bio-model (corresponding to overall costs of approximately US\$ 650). D'Urso [9] calculated the cost for the acrylic to be approximately US\$ 300 and for the bio model to be around US\$ 1000. Lee [21] calculated the costs for a CAD/CAM prefabricated PMMA prosthesis produced in-house to be about US\$ 800. The need of dedicated technicians to survey the CAD/CAM of the bio-model and hardware requirements (when not available in-house) is disadvantageous. Rapid prototyping machines are available for 30,000–250,000 Euros (US\$ 37,000–310,000). Such a machine may serve a variety of disciplines including neurosurgery, maxillofacial and craniofacial surgery, orthopedics, ENT surgery, vascular and basic research in a larger hospital or research institution [2,14,20,24,28,34,38].

Cranioplasty materials other than PMMA modeled so far with the help of CAD/CAM techniques included titanium [4,5,17,18,33], carbon fiber reinforced polymer [26,36] and porous hydroxyl-apatite [10,32]. The handling of these materials requires special expertise that usually is not available in neurosurgical departments. Outsourcing of implant fabrication is expensive. Hydroxyl-apatite implants cost approximately 7000 Euros (about US\$ 8000) [32], implants made from carbon-fiber reinforced polymers are reported to cost 6800 Euros (US\$ 8300) per patient [36].

The technique presented here has many advantages. First, the ability to reconstruct even large or complicated defects with a cosmetically acceptable result; second, the use of an inexpensive material (PMMA) with well-known physical and biological properties; third, the avoidance of contact between implant and nervous tissue during the exothermic polymerization process; fourth, the immediate repeatability of the procedure in case of poor fit of a first implant (due to incongruities or deformation arising during the polymerization process) or in case of fracture of the implant during trimming; fifth, the avoidance of implant deformation during polymerization or sterilization (since not the implant but a model of the defect is sterilized); sixth, the cost reduction associated with the in-house availability of RP technology, and seventh, the prospect to be ready for cranioplasty within 72 h after CT scanning. Our technique can be performed at the fraction of the costs charged by commercial suppliers and does not require the transmission of sensible patient data out of the hospital environment via hard disk or internet.

## 5. Conclusion

PMMA implants fabricated in-house by direct molding using a stereolithographic bio-model of the patient's head are easily produced, fit properly and are inexpensive compared to cranial implants fabricated with similar RP techniques.

## Conflict of interest

None declared.

## Acknowledgement and financial support

None declared.

## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

## REFERENCES

- [1] Agner C, Dujovny M, Evenhouse R, Charbel FT, Sadler L. Stereolithography for posterior fossa cranioplasty. *Skull Base Surg* 1998;8(2):81–6.
- [2] Anderl H, Zur Nedden D, Muhlbauer W, Twerdy K, Zanon E, Wicke K, et al. CT-guided stereolithography as a new tool in craniofacial surgery. *Br J Plast Surg* 1994;47(1):60–4.
- [3] Andrzejak S, Fortuniak J, Wróbel-Wiśniewska G, Zawirski M. Clinical evaluation of the polypropylene-polyester knit used as a cranioplasty material. *Acta Neurochir (Wien)* 2005;147(9):973–6. discussion 976.
- [4] Bhargava D, Bartlett P, Russell J, Liddington M, Tyagi A, Chumas P. Construction of titanium cranioplasty plate using craniectomy bone flap as template. *Acta Neurochir (Wien)* 2010;152(1):173–6. <http://dx.doi.org/10.1007/s00701-009-0394-2>
- [5] Cabraja M, Klein M, Lehmann TN. Long-term results following titanium cranioplasty of large skull defects. *Neurosurg Focus* 2009;26(6):E10. <http://dx.doi.org/10.3171/2009.3.focus091>
- [6] Chrzan R, Urbanik A, Karbowski K, Moskała M, Polak J, Pyrich M. Cranioplasty prosthesis manufacturing based on reverse engineering technology. *Med Sci Monit* 2012;18(1):MT1–6.
- [7] Cooper PR, Schechter B, Jacobs GB, Rubin RC, Wille RL. A pre-formed methyl methacrylate cranioplasty. *Surg Neurol* 1977;8(3):219–21.
- [8] Costantino PD, Friedman CD, Lane A. Synthetic biomaterials in facial plastic and reconstructive surgery. *Fac Plastic Surg: FPS* 1993;9(1):1–15. <http://dx.doi.org/10.1055/s-2008-1064591>
- [9] D'Urso PS, Earwaker WJ, Barker TM, Redmond MJ, Thompson RG, Effenev DJ, et al. Custom cranioplasty using stereolithography and acrylic. *Br J Plast Surg* 2000;53(3):200–4. <http://dx.doi.org/10.1054/bjps.1999.3268>

- [10] Della Puppa A, Mottaran R, Scienza R. Image-guided cranial osteoma resection and bioceramic porous hydroxyapatite custom-made reconstruction in a one-step surgical procedure. Technical notes and illustrative case. *Acta Neurochir (Wien)* 2010;152(1):155-9. <http://dx.doi.org/10.1007/s00701-009-0374-6>
- [11] Durham SR, McComb JG, Levy ML. Correction of large (>25 cm<sup>2</sup>) cranial defects with "reinforced" hydroxyapatite cement: technique and complications. *Neurosurgery* 2003;52(4):842-5. discussion 845.
- [12] Elkins CW, Cameron JE. Cranioplasty with acrylic plates. *J Neurosurg* 1946;3:199-205.
- [13] Eppley BL. Biomechanical testing of alloplastic PMMA cranioplasty materials. *J Craniofac Surg* 2005;16(1):140-3.
- [14] Eufinger H, Wehmoller M, Machtens E, Heuser L, Harders A, Kruse D. Reconstruction of craniofacial bone defects with individual alloplastic implants based on CAD/CAM-manipulated CT-data. *J Cranio-maxillo-fac Surg* 1995;23(3):175-81.
- [15] Gliese M, Handel G, Brawanski A. A simple and cosmetically ideal method large cranioplasty. *Zentralbl Neurochir* 2000;61(3):155-7.
- [16] Gronet PM, Waskewicz GA, Richardson C. Preformed acrylic cranial implants using fused deposition modeling: a clinical report. *J Prosthetic Dent* 2003;90(5):429-33. <http://dx.doi.org/10.1016/s002239130300605x>
- [17] Joffe J, Harris M, Kahugu F, Nicoll S, Linney A, Richards R. A prospective study of computer-aided design and manufacture of titanium plate for cranioplasty and its clinical outcome. *Br J Neurosurg* 1999;13(6):576-80.
- [18] Joffe JM, McDermott PJ, Linney AD, Mosse CA, Harris M. Computer-generated titanium cranioplasty: report of a new technique for repairing skull defects. *Br J Neurosurg* 1992;6(4):343-50.
- [19] Kasprzak P, Tomaszewski G, Kotwica Z, Kwinta B, Zwoliński J. Reconstruction of cranial defects with individually formed cranial prostheses made of polypropylene polyester knitwear: an analysis of 48 consecutive patients. *J Neurotrauma* 2012;29(6):1084-9.
- [20] Knox K, Kerber CW, Singel SA, Bailey MJ, Imbesi SG. Rapid prototyping to create vascular replicas from CT scan data: making tools to teach, rehearse, and choose treatment strategies. *Catheter Cardiovasc Intervent* 2005;65(1):47-53. <http://dx.doi.org/10.1002/ccd.20333>
- [21] Lee SC, Wu CT, Lee ST, Chen PJ. Cranioplasty using polymethyl methacrylate prostheses. *J Clin Neurosci* 2009;16(1):56-63. <http://dx.doi.org/10.1016/j.jocn.2008.04.001>
- [22] Mankovich NJ, Samson D, Pratt W, Lew D, Beumer 3rd J. Surgical planning using three-dimensional imaging and computer modeling. *Otolaryngol Clin North Am* 1994;27(5):875-89.
- [23] Marreiros FM, Heuzé Y, Verius M, Unterhofer C, Freysinger W, Recheis W. Custom implant design for large cranial defects. *Int J Comput Assist Radiol Surg* 2016;11(12):2217-30.
- [24] Muller A, Krishnan KG, Uhl E, Mast G. The application of rapid prototyping techniques in cranial reconstruction and preoperative planning in neurosurgery. *J Craniofac Surg* 2003;14(6):899-914.
- [25] Sanan A, Haines SJ. Repairing holes in the head: a history of cranioplasty. *Neurosurgery* 1997;40(3):588-603.
- [26] Saringer W, Nobauer-Huhmann I, Knosp E. Cranioplasty with individual carbon fibre reinforced polymere (CFRP) medical grade implants based on CAD/CAM technique. *Acta Neurochir (Wien)* 2002;144(11):1193-203. <http://dx.doi.org/10.1007/s00701-002-0995-5>
- [27] Schupper N. Cranioplasty prostheses for replacement of cranial bone. *J Prosthetic Dent* 1968;19(6):594-7.
- [28] Sinn DP, Cillo Jr JE, Miles BA. Stereolithography for craniofacial surgery. *J Craniofac Surg* 2006;17(5):869-75. <http://dx.doi.org/10.1097/01.scs.0000230618.95012.1d>
- [29] Solaro P, Pierangeli E, Pizzoni C, Boffi P, Scalesi G. From computerized tomography data processing to rapid manufacturing of custom-made prostheses for cranioplasty. Case report. *J Neurosurg Sci* 2008;52(4):113-6. discussion 116.
- [30] Spence WT. Form-fitting plastic cranioplasty. *J Neurosurg* 1954;11(3):219-25. <http://dx.doi.org/10.3171/jns.1954.11.3.0219>
- [31] Spetzger U, Vougioukas V, Schipper J. Materials and techniques for osseous skull reconstruction. *Minim Invas Therapy Allied Technol: MITAT* 2010;19(2):110-21. <http://dx.doi.org/10.3109/13645701003644087>
- [32] Staffa G, Nataloni A, Compagnone C, Servadei F. Custom made cranioplasty prostheses in porous hydroxy-apatite using 3D design techniques: 7 years experience in 25 patients. *Acta Neurochir (Wien)* 2007;149(2):161-70. <http://dx.doi.org/10.1007/s00701-006-1078-9>. discussion 170
- [33] Stoodley MA, Abbott JR, Simpson DA. Titanium cranioplasty using 3-D computer modelling of skull defects. *J Clin Neurosci* 1996;3(2):149-55.
- [34] Tek P, Chiganos TC, Mohammed JS, Eddington DT, Fall CP, Ifft P, et al. Rapid prototyping for neuroscience and neural engineering. *J Neurosci Methods* 2008;172(2):263-9. <http://dx.doi.org/10.1016/j.jneumeth.2008.03.011>
- [35] van Putten Jr MC, Yamada S. Alloplastic cranial implants made from computed tomographic scan-generated casts. *J Prosthetic Dent* 1992;68(1):103-8.
- [36] Wurm G, Tomancok B, Holl K, Trenkler J. Prospective study on cranioplasty with individual carbon fiber reinforced polymer (CFRP) implants produced by means of stereolithography. *Surg Neurol* 2004;62(6):510-21. <http://dx.doi.org/10.1016/j.surneu.2004.01.025>
- [37] Yacubian-Fernandes A, Laronga PR, Coelho RA, Ducati LG, Silva MV. Prototyping as an alternative to cranioplasty using methylmethacrylate: technical note. *Arq Neuropsiquiatr* 2004;62(3b):865-8. doi:S0004-282x2004000500023.
- [38] zur Nedden D, Knapp R, Wicke K, Judmaier W, Murphy Jr WA, Seidler H, et al. Skull of a 5,300-year-old mummy: reproduction and investigation with CT-guided stereolithography. *Radiology* 1994;193(1):269-72. <http://dx.doi.org/10.1148/radiology.193.1.8090905>