THE PUBLISHING HOUSE
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BIOMATRIALS USED IN CRANIOPLASTY, NEW ASPECTS AND PERSPECTIVES

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Accepted 26 July 2019

This article presents an overview regarding different material and biomaterials used in cranioplasty from some points of view: chemical and physical properties and their interaction in medical process of cranioplasty, biomaterials used in custom made implants versus ready to use and customizable intra-operative materials made with different manufacturing methods (3D printing, CNC milling and drilling and sintering) and our perspective about them in comparison. Almost all custom made implants are using currently a primary acquisition of data like CT scanning by a certain protocol that has to be respected to be useful for a future 3D reconstruction and they respect exactly the bone defect. On the other hand the other biomaterials can be raw materials (cements) or ready to use (mesh, plates, screws) in OR for cranioplasty and these are "manufactured" (mixed, molded, cut, bended, screwed, adjusted) by the surgeon during intervention having their approximate size and shape, their potential risk, including infection and represents a true artwork made by a human against pressure of time and material properties.

Key words: Cranioplasty, Peek, Titanium, Bioverit, Reconstruction, Biomaterials.

INTRODUCTION

Cranioplasty is defined as the surgical intervention performed to repair cranial defects following trauma, surgical decompression, tumour surgery, congenital anomalies or growing skull fractures. Its main purpose is to restore function and anatomical structure of the skull. The implications of cranioplasty are psychological, aesthetic, functional, social and financial. The history of cranioplasty dates back to 7000 BC with archaeological evidence[1,2] supporting the use of both inorganic and organic materials. Although many methods have been described there is little consensus regarding the optimal solution for such cases.

In present are still debates regarding:

1. Different biomaterials as: metallic, ceramic, polymer, resins, synthetics miming bone structure (HA–hydroxyapatite or βTCP), allografts (human donor), Xenografts (animal derived material), autografts (self-donor).

2. Manufacturing methods: preparing in OR during intervention (cements, mesh, plates, screws, sutures, other fixation systems) or PSI (Patient Specific Implants) that are custom made implants for one specific case did only once, ready to be implanted.

3. Risk of infection. Depending on materials, manufacturing method (PSI or to be done during intervention), fixation system (metallic, resorbable, sutures), surrounding tissue involved (temporal muscle) position on cranium (FTP: frontal-temporal-parietal, or FO: frontal – orbital and other possible position) and re-interventions after failed primary cranio-plasty or other secondary complications.

4. Timing of cranioplasty post craniotomy: short (1 month), medium (1–3 months), long-term (after 6 months).

MATERIALS AND METHODS

Present study represent a comparison between different types of materials used in cranioplasty and used information collected during last 9 years from:

1. A multicenter cohort clinical study made in 10 hospitals in Romania;

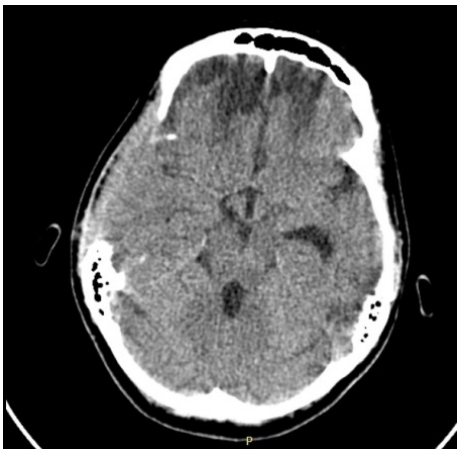
2. Medical and technical literature about biomaterials for cranioplasty.

Regarding clinical part we started a multicenter cohort study on patients with cranial defects of multiple etiologies (trauma, decompression, tumour surgery, etc.) operated in 10 hospitals having enrolled in this study a total of 50 patients from which 16 were female, 34 were male, 22 from urban and 28 from rural area of Romania, aged between 5–68 years old. Regarding etiologies: 31 were trauma, 16 were decompression and 3 were tumor. In all patients during the surgery were repaired the cranial defects using Patient Specific Implants made by 3D printing and CAD, CAM manufacturing (CNC milling and drilling) methods using specific data obtained from the patient's 3D CT reconstruction using a very strict scanning protocol.

CT – scan protocol

Algorithm	optimised for bone
Contrast material	no
Matrix	at least 512 x 512 Pixel
Gantry Tilt	no
Change of thickness	no
Change of spacing	no
Patient Position	back position preferred
Patient Orientation	head first
Thickness Orientation	axial preferred
Slice thickness (Z)	1 mm (reconstructed)
Pixel resolution (X,Y)	0.5 – 0.7 mm
Field of View	quadratic
Table feed (Spiral CT)	<3 mm per Rotation

A



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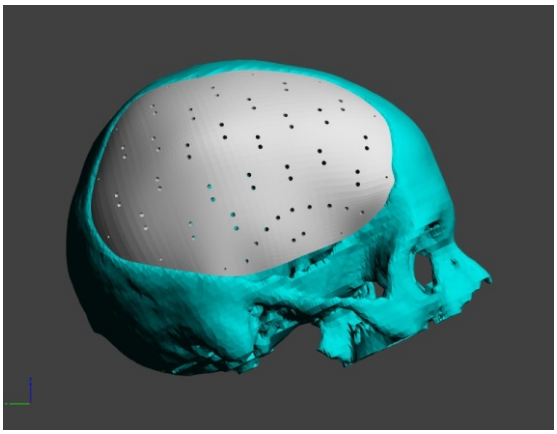

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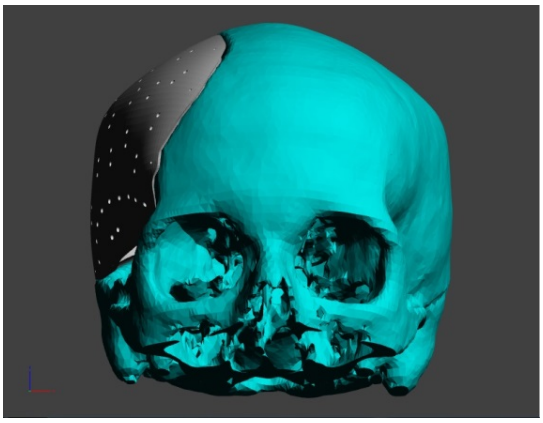

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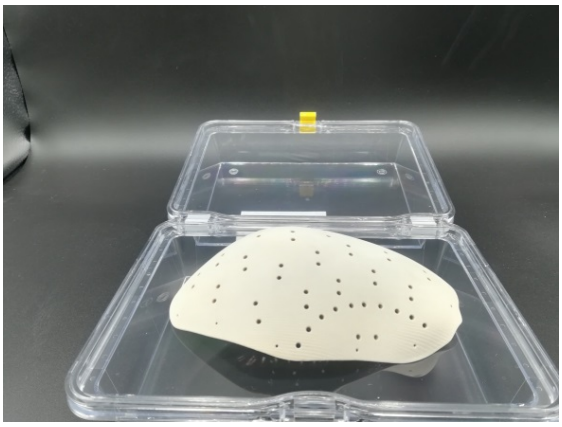

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Figure 1. A – CT scan protocol used to create specific data to be converted in a 3D dynamic model, B – Slice from CT (DICOM file), C – 3D reconstruction file (right view), D – 3D reconstruction file (frontal view), E – Patient Specific Implant from PEEK, for surgery (follow to be sterilized), F – PSI from PEEK, implanted in cranial bone defect with Titanium fixation system[12].

The follow up varies from 1 to 9 years. Materials used for implants: Peek, Titanium Alloy and Bioverit II (ceramic glass). Distribution of implant materials from our study was: 45 cases with Peek, 4 cases with Titanium Alloy, 1 case with Bioverit II.

Procedure:

1. In almost all cases, the procedure is the same. DICOM data files are collected and archived into a zip file and sent encrypted, through a secure transfer platform, with a dynamic password, that has to be communicated each time, to recipients and that is internet safe and keeps all info strictly confidential.

2. Files are extracted, verified if scanning protocol was respected and if they are qualified to be transformed in ".stl" extension files or other software extension used to see bone defect, compare it with standard anatomic models, with contra-lateral side of the same patient .

3. Create a 3D dynamic model of cranium with all defects and of patient specific implant that has to fit perfectly into that defect.

4. The 3D model (pdf file with 3D media option activated) is sent and presented by manufacturer directly to the surgeon with several comments regarding: surrounding soft tissue, sizes, distances, thickness and a lot of other parameters, including material together with an approval letter that has to be stamped and signed by the surgeon.

5. The surgeon will reply (in written) to the manufacturer with its comments regarding all of the above and in some steps will conclude if he agrees or not, on the proposed 3D model.

6. If the response is affirmative and all legal and financial issues are agreed upon by all parts, the manufacturer will start to produce the implant, respecting all safety and regulations of EU, regarding Patient Specific Implants.

7. That will be delivered in the country of the surgeon, directly to its hospital OR during a period of 5–15 days. In some emergency cases, the implant can be delivered within 48 hours, with a set of legal documents and a passport for the implant; the passport contains all of the important info that patient has to have, after surgery. Implant came unsterile and very well packaged; it will be sterilized to 134°, 1–2 cycles 20 minutes, 24–48 hours prior the day of surgery.

Depending on the size of bone defect, anatomical area, position on cranium and risk of infection (frontal, sinus, zygomatic area) the surgeon will decide upon the best material for the implant (Titanium alloy, Peek or ceramic glass) and what fixation systems are best for the implant. The most common and used materials are: non-resorbable suture 2.0, Titanium, Peek or bio-resorbable craniofix type implants that use a special tool for anchoring and fixation, Titanium 2-4-6 holes plate 1.3/1.6/2.0 mm and 1.3/1.6/ 2.0 mm, different designs (straight, double-Y plate, adjustable mesh or pre-contoured) screws locking or non locking 3–5 mm length.

HISTORY AND PRESENT KNOWLEDGE IN BIOMATERIALS FOR CRANIOPLASTY

The history of cranioplasty dates back to 7000 BC with archeological evidence supporting the use of both inorganic and organic materials. Although many methods have been described there is little consensus regarding the optimal solution for such cases.

Further we remind cranioplasty materials used along the history till present with some historical data and facts as written in literature but also some physical properties studied of some of them (PEEK, Titanium, Bioverit II).

AUTOGRAFT

First recorded use of auto grafts for cranioplasty was in 1821 by surgeon Walther[2]. In 1889 Seydel used Tibia for facial reconstruction and after that in 1906 Beck used temporal muscle and fascia. Rib bone was used in 1915 by Kapis and Brown (1918) and in 1914 Mauclaire used iliac and sternal bone.

Advantages: It has an increased osteo-conduction, once it is accepted but requires good blood supply for osteo-integration. Autograft is preferred against any foreign material. It is known in history the method of contra lateral resection from own skull known as "split-skull cranioplasty" and it can be stored extracorporeal or through abdominal preservation.

Disadvantage: Inner matrix of bone can be easy destroyed during sterilization and autoclaving and provides an increased rate of resorbtion (2–35% adults and 50–60% children).

ALLOGRAF AND XENOGRAFT

Allograft represents bone harvested from human donors. First case was reported use by

Morestin 1915. In 1682 Van Meereken used canine bone, in 1893 Schmidt used rabbit bone, in 1898 Grekopf[2] reported the use of bovine bone.

Disadvantage: They have high resorption rates and they provide an unwanted immune response.

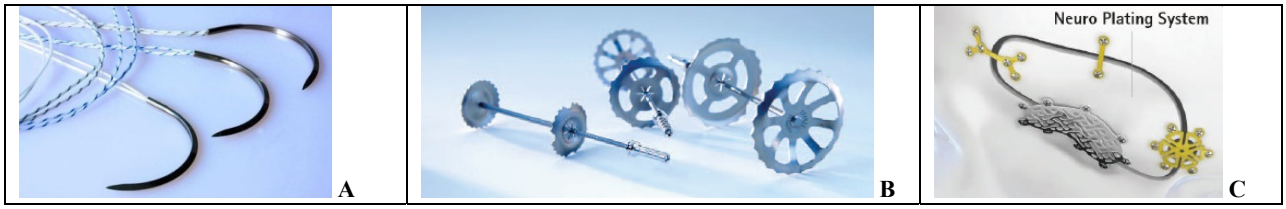

Figure 2. (A) suture, (B) Titanium or resorbable craniofix fixation type system, (C) plates, mesh different designs and screws[11].

Table 1

Cranioplasty Biomaterials – Historical dates

No.	Manufacturer/ Surgeon	Material used
1	Petronius (1565)	Gold Plates
2	Fallopius (1600)	Bone, Gold Plates
3	Van Meekeren (1670)	Canine bone
4	Walther (1821)	Auto graft
5	Macewen (1888)	Replantation
6	Burren	Bone Button
7	Seydel (1889)	Tibia
8	Muller (1890)	Other table skull
	M. Hunter (1910)	Titan
9	Westerman (1916)	Sternum
10	Brown (1917)	Rib
11	Dambrin (1919)	Cadaver
12	Maclenan (1920)	Scapula
13	Fagarasanu (1937)	Split Rib
14	Von Hintestoisser	Celluloid
15	Booth	Aluminium
16	Cornioley (1925)	Platinum
17	Kleinshmidt (1940)	MMA
18	Zander (1940)	PMMA
19	Invibio (1998)	PEEK
20	Beau & Grossmann (2000)	Bioverit II

ACRYLIC – MMA AND PMMA

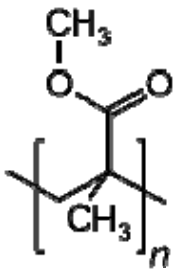

Figure 3. Graphical chemical structure of PMMA monomer.

Developed in an independent laboratory in 1928 by chemists like William Chalmers, Otto Röhm and Walter Bauer, was launched in the market first time in 1933 by Rohm and Haas Company. It was discovered by Zender in 1940. Chemical formula: $(C_5O_2H_8)n$–monomer. Is Poly-methyl-methacrylate (PMMA) is a polymerized ester of acrylic acid. Commercial it is provided packed sterile. It has a density of 1.19 g/cm^3. Burn temperature in presence of air 460°

Advantage: PMMA is one of the most used materials in reconstruction. Provides good compression and a certain mechanical resistance, it is non-allergenic, radiopaque (when enriched with Barium Sulfate). Can be mixed with antibiotic: Gentamicin and Vancomicin that will helps against infection.

Disadvantage: Low to zero osteointegration and it is breakable at a strong impact.

CERAMICS

Hydroxyapatite has a crystalline compounds that have a design similar to that of the bone. Ray and Ward tested in 1951 hydroxyapatite (HA) in cranial reconstruction in animals.

Advantage: Good osteointegration, low foreign body reaction, good cosmetic results.

Disadvantage: High infection rate, very fragile, shatter risk, reduced malleability.

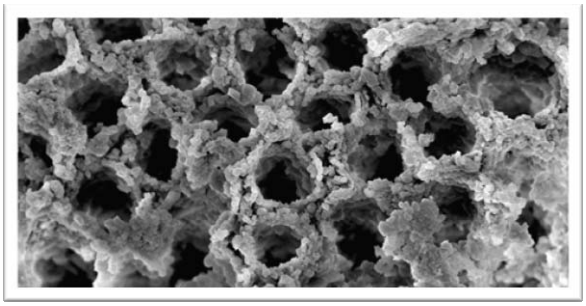

Figure 4. Crystals of hydroxyapatite (HA).

TITANIUM

Most of implants are from Titanium Alloy with formula: Ti_6Al_4V

Use of Titanium was World War 2 it has developed as a superior chemical formula and alloy after 1980s. It is biocompatible, non-corrosive and has a low infection risk. It can be used to create Patient Specific Implants after a 3D reconstruction through: sintering, milling and drilling and 3D printing. *Disadvantage*: It has a low osteointegration, some minor risks regarding MRI even most manufacturers offer MRI compatibility certificates and it is heat sensible. When shaped in a plate or custom- made implant has a reduced malleability. If it is presented like a mesh plate with a lot of holes along its design it has a reduced mechanical resistance.

POLYMERS (PEEK)

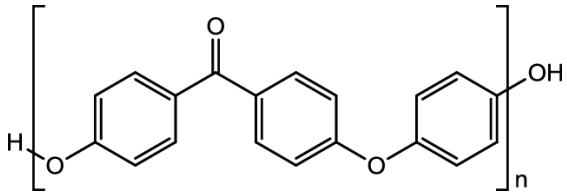

Figure 5. Chemical formula of PEEK.

Medical semi-crystalline polymer with a linear poly-aromatic structure. Scientific name: poly (oxy-1,4-phenyene-oxy-1, 4-phenyene)[6]. Starting with 1998, PEEK (Polyetheretherketone) was developed first for spinal surgery and for the production of hip prostheses by a company called INVIBIO. This days PEEK is used for man types of reconstructions including cranioplasty.

Advantage: It is inert and non-degradable. It shows resistance comparable to that of the cortical bone, it is MRI compatible, has a good strength, it is light weight and it is radio transparent. It can be used to create Patient Specific Implants after a 3D reconstruction through: sintering, milling and drilling and 3D printing.

Disadvantage: It is not osteo-conductive and it is moderate to high expensive in comparison with other biomaterials[8].

Physical properties:

- Colour – Natural
- Melt Viscosity: 0.16–0.44 kNs/m^2
- Density: 1.3 G cm^{-3}
- Tensile strength: 100–108 MPa (ksi)
- Tensile elongation: 25–40 %

BIOVERIT (GLASS-CERAMIC)

Chemical formula: SiO_2-Al_2O_3-MgO-Na_2O-K_2O-F

BIOVERIT II is a non-resorbable glass ceramic composed of Phlogopite – and Apatite crystals (approx. 60%), embedded in an alum silicate glass matrix (approx. 40%).

It is a biomaterial used since 1982 to manufacture medical implants[3]. Since 2000 was used to create cranial reconstruction implants.

Advantage: It is biocompatible (it is proved fibroblast growth), bio inert and corrosion resistant. It has the similar heat conduction properties like natural bone has. It is moldable during surgery, MRI/ CT compatible, radiolucent and allows seam sterilization. It is common used in CMF surgery for facial cranial reconstruction because its antibacterial properties[3].

Physical properties: It is white, no smell, and solid, doesn't vaporize and can be moulded with conventional tools. It can be used to create Patient Specific Implants after a 3D reconstruction through CNC milling and drilling.

Disadvantage: It is breakable at a strong mechanical impact.

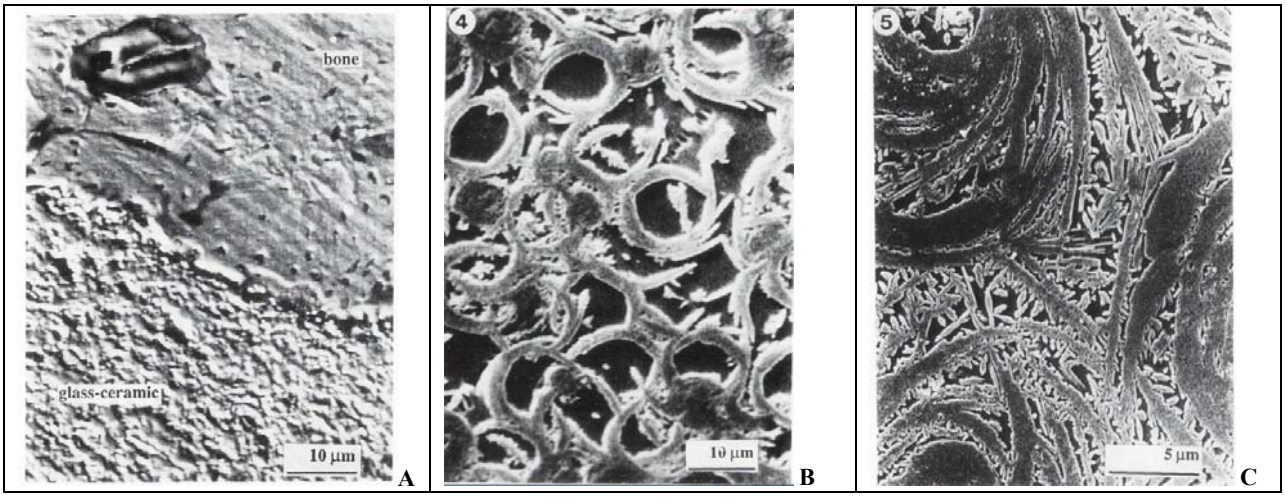

Figure 6. A –Interface in (Guinea pig) between bone and glass-ceramic type BIOVERIT II at 1 year after implantation. B – Curved crystals of Phlogopite from glass-ceramic BIOVERIT II, C – Precipitation of mica-cordierite in crystals of BIOVERIT II.[12]

Figure 7. Implant PSI (Patient Specific Implant) from: A – PEEK , B – Bioverit II, C – Titanium[12].

Table 2

We present below a table of different cranioplasty materials regarding: Mechanical strength (resistance), Biological properties (Osteoinduction, Osteointegration), Risk of infections after implantation, Effectiveness against an ongoing infection, Size of defect that can be covered, Radiolucency, Compatibility with CT and MRI exploration and Cost

Material	**AUTOGRAFT**	**PMMA**	**HA**	**CERAMIC BIOVERIT)**	**PEEK**	**TITANIUM**	**TITANIUM MESH / PLATE & SCREWS**
Mechanical strength (resistance)	high	low	low	moderate	high	high	high
Biological properties (Osteoinduction, Osteointegration)	high	no	moderate to high	no	no	no	no
Risk of infections after the implantation	high	high	high	low	moderate	high	high

Effectiveness against an ongoing infection	low	high (Antibiotic option)	moderate to high (with antibiotic	low	low	low	no
Size of defect	medium & large	small & medium	small	small	large	large	small & medium
Radiolucent	no	yes	no	yes	yes	no	no
CT/MRI compatible	yes	yes	yes	yes	yes	yes	yes
Cost	low	low	moderate to high	moderate to high	high	moderate to high	moderate

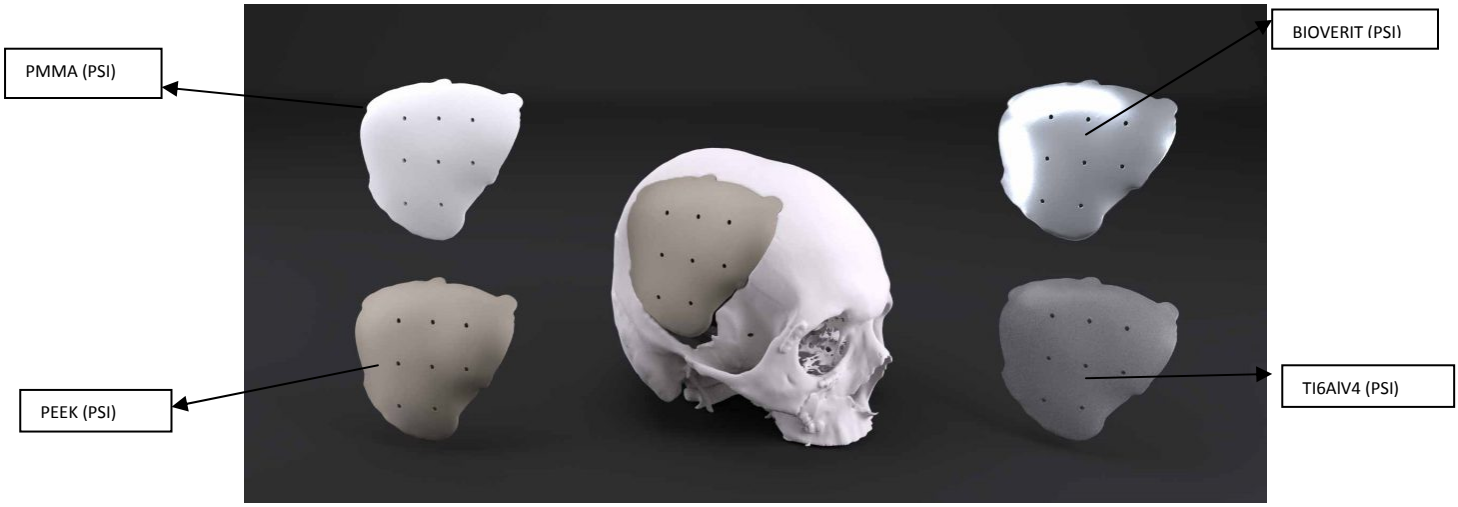

Figure 8. Intracranial implants PSI (Patient Specific Implants – custom made) from different materials, using the same CT acquisition data[7,9].

Using the same procedure as described above with:

1. Data acquisition;
2. Convering files into stl files for a special software like MIMICS 3D (MATERIALIZE USA);
3. Create 3D model;
4. Communicate to surgeon;
5. Obtain feedback and approval from surgeon;
6. Manufacturing PSI (Patient Specific Implant) in present is possible to create for the same cranial defect, various implants from different materials like: PMMA (pre shaped) with or without antibiotic, PEEK, Titanium Alloy(Ti_6Al_4V), Bioverit II (glass-ceramic) that will be sterilized and used with success in cranioplasty.

RESULTS AND DISCUSSION

One problem in cranioplasty is timing during intervention. What do you use, prefer or consider efficient in a standard cranioplasty. From these choices derives a series of questions and answers of neurosurgeon:

- To us Autograft? Yes is from the same patient but it has a risk of resorption.
- Allograft? There are some legal problems with human donors. Why Xenograft? Are old fashion and not accepted anymore by medical community.
- PMMA? Yes, is cheap, ready to use but you have to prepare it into surgery and have to take into account polymerization temperature (50–67°), time to loose with mixing, melting, and final structure is approximate like defect but not perfect and breakable. Can go in future to fail and possible infection.
- Pre-shaped PMMA? It can be a PSI like Peek and others an you can even enrich it with antibiotic. Has problem with modelling during intervention and it is also breakable.
- Why HA (hydroxyapatite)? It is expensive, has one of the best matrixes for osteo-integration, but is also breakable and you can cover small defects.
- Why Bioverit II? It is a PSI more used in CMF surgery or in cranioplasty with bones in calvarias – face junction with a high infection risk. It is breakable at a high force impact.

Table 3

Comparison between biomaterials regarding which can be offered like PSI,
if they require a Pre-operative Model and which have to be customized intra operative and which are ready to implant

Material	AUTOGRAFT	Allograft and Xenograft	PMMA	Pre-shaped PMMA	HA	CERAMIC (BIOVERIT)	PEEK	TITANIUM	TITANIUM MESH / PLATE & SCREWS
Patient Specific Implant (ready-to use)	no	no	no	yes	no	yes	yes	yes	no
Preoperative 3D model	no	no	yes	yes	no	yes	yes	yes	no
To be customized in surgery	yes	yes	yes	no	yes	no	no	no	yes

– PEEK (Polyether-ether-ketone) an be offered at demand as a PSI, perfect shape for bone defect, it will fit perfect, it is light weight and very resistant, inert, non-breakable, can be shaped during surgery and also expensive.
– Titanium alloy (Ti_6Al_4V) can be a perfect PSI, very strong, not moldable during surgery in case needed, very good heat conductor and MRI compatible

Regarding the clinical study: There were a total of 50 patients treated with Patient Specific Implant that proved significant aesthetic, functional and psychological improvements after the cranioplasty surgery. Minor complications occurred in several cases, that were related to cranioplasty fixation systems and scalp complications (related to initial trauma), and two cases of wound infection (one related to the type of suture used and the other wound contamination without suture defect). There were no fatalities and no long-term complications.

Versus our study with PSI, mainly because of costs most of cranioplasty were performed with PMMA In very few case surgeons used Cranioplasty PMMA, most of surgeons used orthopaedic PMMA.

CONCLUSION

- Custom 3D implants for cranial reconstruction are a safe and viable solution that has been available for some time.
- Cranioplasty can not only restore the integrity, the continuity of skull and the previous appearance, but also stabilize the intracranial pressure and create a intracranial stable state that facilitates the metabolism of brain tissues, restores the function of cranial nerves, re-establishes the brain protection and reduces the adverse consequences caused by the defect.
- Superior aesthetics and good functional outcomes can be achieved with a 3D patient specific implant (where other common methods fail: cement, PMMA broken implants, etc.).
- A Patient Specific Implant is made 1 time for 1 single Patient and involves multiple parties, each with their own responsibilities: the patient ant his family, the surgeon, the hospital, the manufacturer, the project manager.
- Our study proves the fact that in present in Romania most cranioplasty interventions are performed with PMMA in many cases a non-specific for cranioplasty PMMA *versus* PMMA method, PSI can be safely implemented even in surgical centres with no prior experience, using 3D custom made implants.
- Nevertheless, the financial aspect of using such an implant is the main factor that negatively influences the addressability of such a technique to the general public. At this time Patient Specific Implants in Romania are paid by patients and are expensive, but very reliable and effective at the same time.
- We can appreciate that the number of cranioplasty cases done with PSI (Patient Specific Implants) would be 10 times more in Romania, if a National Program for Neurosurgery would cover the costs of such implants.
- This method would also increase the economy of the Ministry of Health's budgets, due to a reduced period of post-op recovery and minimal rate of re-interventions and complications.

List of abbreviations:

HA – Hydroxyapatite
PSI – Patient Specific Implant
βTCP – Beta –tricalcium phosphate
MRI – Magnetic resonance
PMMA – Poly-methyl-methacrylate
PEEK – Polyethil – ether – ether – ketone
CNC milling and drilling – Computer numerical control (CNC) is programmed code that represents instructions for precise movements to be carried out by machines. Milling is the process of cutting and drilling material (like wood, polymer or metal).

REFERENCES

1. Shah AM, Jung H, Skirboll S. *Materials used in cranioplasty: a history and analysis*. Neurosurg Focus 2014;36(4):E19
2. Aciduman A, Belen D: *The earliest document regarding the history of cranioplasty from the Ottoman era*. Surg Neurol 68:349–353, 2007.
3. Mohammed E. Elsalanty, David G. Genecov, *Bone Grafts in Craniofacial Surgery,* Craniomaxillofac Trauma Reconstr. 2009 Oct; 2(3): 125–134. Republicat 2009 Apr 14. doi: 10.1055/s-0029-1215875.
4. Aydin S, Kucukyuruk B, Abuzayed B, Aydin S, Sanus GZ: *Cranioplasty: review of materials and techniques*. J Neurosci Rural Pract 2:162–167, 2011.
5. Oliveira AMP. *Efeitos da cranioplastia em doentes submetidos à craniectomia descompressiva: avaliação anatômica, neurológica e da hemodinâmica encefálica* [Thesis]. São Paulo: Faculdade de Medicina da Universidade de São Paulo; 2015.
6. J. Jonkergouw, S.E.C.M. van de Vijfeijken, E. Nout, T. Theys, E. Van de Casteele, H. Folkersma, P.R.A.M. Depauw, A.G. Becking, *Outcome in patient-specific PEEK cranioplasty: A two-center cohort study of 40 implants*, Journal of Cranio-Maxillofacial Surgery 44(9)· July 2016 doi: 10.1016/j.jcms.2016.07.005.
7. Haug RH, Adams JM, Conforti PJ, *et. al.*, *Cranial fractures associated with facial fractures*, J Oral Maxillofac Surg, 1994; 52(7):729-33.
8. Rish BL, Dillon JD, Meirowsky AM, Caveness WF, Mohr JP, Kistler JP, *et al.*, *Cranioplasty: A review of 1030 cases of penetrating head injury*. Neurosurgery. 1979; 4:381–5.
9. Blake DP. *The use of synthetics in cranioplasty: A clinical review*. Mil Med. 1994; 159:466–9.
10. Grant FC, Norcross NC. Repair of cranial defects by cranioplasty. Ann Surg110:488-512, 1939.
11. AESCULAP, BRAUN Contributors (Brochure No. C08802 0714/0.5/3), *Aesculap Craniofix® 2, Cranial Fixation System, 2017.*
12. 3DI Contributors (Brochure, 3di Prospekt, Rev. 1, 17.10 2016), *3DI Patient Specific Skull Implants*, 2016.
13. INVIBIO Contributors (Brochure – *PEEK, Typical Material Properties*), 2013.