

RESULTS OF CRANIOPLASTY USING INDIVIDUAL TITANIUM IMPLANTS

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Background. Despite its long history, cranioplasty remains a topical problem of neurosurgery, due to the increasing number of traumatic brain injury, the consequences of which are the main driver in preserving the population of patients with postcraniectomy skull defects. As a rule, these defects are extensive, and the use of individual implants in these cases is the method of choice. Over the past 5 years, the use of products created by medical additive manufacturing has increased, in this regard, the assessment of long-term results of surgical interventions with their use is an actual issue of modern medicine.

Aim. to evaluate the results of surgical treatment of patients with skull defects of various etiologies using individual titanium implants made by three-dimensional printing.

Materials and methods. The study analyzed 94 cases of cranioplasty using individual titanium implants made by three-dimensional printing using DMLS (Direct Metal Laser Sintering) technology. The minimum follow-up period was 12 months from the moment of the intervention. Traumatic brain injury and its consequences was the dominant cause of skull bone defects ($n = 56$, 59.6 %). The average area of defects in the study group was 99.2 ± 43.4 cm². For men ($n = 53$), this parameter corresponded to 106.7 ± 44.7 cm², for women ($n = 41$) – 89.5 ± 40.1 cm².

Results. The total number of complications in the study group was 12 (12.7 %) cases, of which 5 (5.3 %) cases were recorded during the in hospital stay of patients, 7 (7.4 %) – during outpatient follow-up. One complication was not related to the performed surgical intervention. Removal of the implant was required in 7 (7.4 %) cases. The terms of implant removal varied from 0 to 14 months from the moment of the performed intervention. The survival rate of individual titanium implants for more than 12 months was 92.6 %.

Conclusion. The data on the presence of complications after cranioplasty vary from study to study, while the results of reconstructive interventions performed using individual titanium implants are of significant interest, the use of which has increased significantly over the past five years due to the introduction of additive medical production into clinical practice.

Keywords: cranioplasty, cranial defect, three-dimensional printing, follow-up, complications

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INTRODUCTION

Despite its long history, cranioplasty remains a pressing issue in modern neurosurgery. In general, cranial defects are mostly artificial and are formed during neurosurgical interventions accompanied by removal of certain parts of the cranial bones. The main reasons for craniectomies are severe or, less frequently, moderate brain injury; intracranial hemorrhages of varying causes: intraparenchymal hypertensive, subarachnoid due to cerebral aneurysm ruptures; acute cerebrovascular diseases (ischemic stroke) accompanied by brain edema and dislocation; oncological diseases affecting cranial dura and bones [1–4]. Multiple epidemiological studies show annual increase in the number of patients with brain injuries [5–8], and consequences of surgi-

cal interventions for their treatment constitute the most cases of post-craniotomy defects of the cranial bones [1–4].

During management of the acute consequences of disorders which required performance of craniotomy and patient transfer into the recovery period, it is necessary to close the existing defects of cranial bones as their persistence can have negative effects: development of trephination syndrome, brain matter collapse, absence of protection from direct mechanical impacts, as well as psychological problems due to esthetic defects in appearance [9, 10].

Due to the introduction of implants produced using additive manufacturing, the number of studies on the use of individualized implants has been growing annually. Currently, medical 3D printing is the most technologically

advanced method of production of individualized implants as it allows to eliminate such interim items as press forms and anatomical models. At the moment in Russia, technology of metal printing from titanium alloy powder is available which can be performed by direct metal laser sintering (DMLS) or electron beam melting (EBM) [11]. Powder of titanium-aluminum-vanadium alloy is used as raw material, and completed implants are chemically identical to implants produced using traditional molding.

In accordance with the stated above, the **aim of the study** was formulated: to evaluate the outcomes of surgical treatment of patients with cranial defects of varying etiology using individualized titanium implants manufactured by 3D printing.

MATERIALS AND METHODS

Primary endpoint: survival of individualized titanium implant during follow-up period of at least 12 months after cranioplasty.

Secondary endpoints: sex, age, cause of cranial defect, area of cranial defect, operative time, blood loss, type and number of postoperative complications, inpatient bed-days.

Inclusion criteria: presence of cranial defect, age >18 years, signed informed consent to participate in the study,

cranioplasty performed using individualized titanium implant manufactured by 3D printing.

Exclusion criteria: follow up <12 months since surgery, absence of data on patient's condition after discharge from the hospital, patient's refusal to participate in the study.

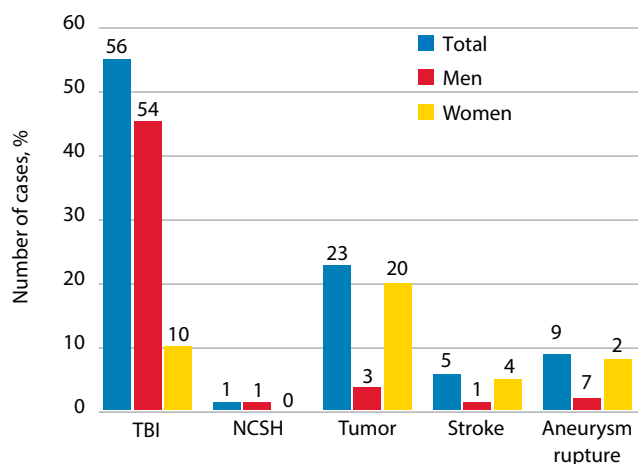
Between 2016 and 2021 at the Neurosurgical Division No. 1 of the Novosibirsk Scientific Research Institute of Traumatology and Orthopedics named after Ya.L. Tsivyan, 129 cranioplasties using individualized implants manufactured by 3D printing were performed. One hundred (100) patients complied with the inclusion criteria for the study approved by the institute's local ethical committee. Among the patients, 2 had bilateral defects. Every operation with 1 implant was considered a separate clinical case, therefore, 102 observations were approved for analysis. However, at 12 months and beyond after cranioplasty contact was lost with 8 patients who had unilateral cranial defects. Therefore, for evaluation of treatment outcomes in accordance with the study criteria, 94 clinical cases were selected. Descriptive characteristics for the main studied parameters are presented in Table 1.

The main cause of cranial defect formation were brain injuries and their consequences ($n = 56$, 59.6 % of the total number). Distribution of clinical cases depending on the cause of cranial defect is presented in the figure.

Table 1. Data of the main study parameters

Parameter	Total ($n = 94$)	Men ($n = 53$)	Women ($n = 41$)
Age, years			
$M \pm SD$	42.2 ± 14.5	36.7 ± 12.5	49.2 ± 14.1
Min–max	19–75	19–69	25–75
Me [Q_1 ; Q_3]	37.5 [31; 53]	34 [29; 42]	51 [37; 60]
95 % CI	39.2–45.1	33.3–40.2	44.7–53.6
Defect square, cm ²			
$M \pm SD$	99.2 ± 43.4	106.7 ± 44.7	89.5 ± 40.1
Min–max	17.8–314	23.2–314	17.8–193.9
Me [Q_1 ; Q_3]	99.2 [70.6; 121.9]	102.7 [89.1; 126.9]	89.3 [61.8; 120.8]
95 % CI	90.3–108.1	94.4–119.0	76.8–102.1
Operation time, min			
$M \pm SD$	107.4 ± 52.3	118.0 ± 55.7	93.7 ± 44.6
Min–max	25–300	50–300	25–220
Me [Q_1 ; Q_3]	90 [70; 130]	100 [75; 155]	90 [70; 115]
95 % CI	96.7–118.1	102.7–133.4	79.6–107.7
Blood loss, ml			
$M \pm SD$	175.6 ± 126.9	202.1 ± 138.2	141.5 ± 102.3
Min–max	20–800	30–800	20–400
Me [Q_1 ; Q_3]	150 [100; 200]	160 [100; 200]	100 [100; 150]
95 % CI	149.7–201.6	163.9–240.2	109.2–173.7
In hospital stay, days			
$M \pm SD$	12.1 ± 11.9	13.7 ± 15.5	9.9 ± 2.4
Min–max	4–95	4–95	6–17
Me [Q_1 ; Q_3]	10.5 [8; 12]	11 [8; 13]	10 [8; 12]
95 % CI	9.6–14.5	9.4–17.9	9.2–10.7
Follow up period, months			
$M \pm SD$	36.6 ± 16.7	35.4 ± 17.2	38.1 ± 16.2
Min–max	12–64	12–63	12–64
Me [Q_1 ; Q_3]	36 [24; 51]	35.5 [19; 51]	36 [25; 50]
95 % CI	33.1–40.0	30.6–40.2	32.9–43.2

Note. $M \pm SD$ – mean and standard deviation of the mean; Me [Q_1 ; Q_3] – median, lower and upper quartiles; 95 % CI – 95 % confidence interval.



Distribution of clinical cases depending on the cause of the skull defect formation. TBI – traumatic brain injury; NCSH – nontraumatic chronic subdural hematoma

Mean defect area in the study group ($n = 94$) was $99.2 \pm 43.4 \text{ cm}^2$. In males ($n = 53$), this parameter was $106.7 \pm 44.7 \text{ cm}^2$, in women ($n = 41$) – $89.5 \pm 40.1 \text{ cm}^2$; there were no significant differences in defect area between the subgroups ($p_U = 0.15$). Distribution of defects per area (in accordance with the clinical classification developed at the N.N. Burdenko National Medical Research Center of Neurosurgery [12] and recommended by the Russian Association of Neurosurgeons) is presented in Table 2.

After recruitment the patient signed voluntary informed consent for participation in the study. At the stage of pre-operative outpatient examination, all patients underwent multi-slice computed tomography. The results were used to design and manufacture individualized titanium implants (LOGIKS Medical Systems, Russia) using 3D printing. The implants were manufactured on the EOS M 290 printer (EOS, Germany) using DMLS technology from titanium alloy powder Ti-6Al-4V (production label Ti64ELI) (EOS GmbH, Germany).

Surgical intervention was performed in traditional manner. If needed, plastic surgery of the dura mater was performed using autologous tissues (aponeurosis, periosteum) or synthetic transplants (Lyoplast® Onlay, Neuro-Patch®, Dura Soft Reperen®); if additional water-tight closure of the dura mater was necessary, fibrin sealant was used (Elicel™). In cases when diastasis between the dura mater and internal surface of the individualized titanium implant was larger than 15 mm, the cavity was packed with autologous fatty tissue extracted from the anterior abdominal wall of the patient during cranioplasty. The titanium implant was installed into the defect location and fixed in place with 5 mm self-drilling screws (Matrix Synthes®, Osteonic®, Conmet); active aspiration drain was installed under the cutaneous aponeurotic flap. Control multi-slice computed tomography was performed in all patients during the first 24 hours after surgery. In cases accompanied by complications during hospital stay, the number and type of imaging studies were determined based on the clinical picture.

Table 2. Skull defects distribution by area, n

Defect type	Total	Men	Women
Small (<10 cm ²)	0	0	0
Medium (10–30 cm ²)	5	1	4
Large (30–60 cm ²)	11	6	5
Extensive (60–120 cm ²)	49	28	21
Giant (>120 cm ²)*	29	18	11

*The added criterion of S.A. Chobulov research [13].

Discharge from the hospital for the most patients was performed between day 4 and day 12 after surgery. At outpatient stage, the patients underwent control exams at 3, 6 and 12 months after surgery and then 1 time a year 12 months after the last check-up. In cases of complications, examination schedule was changed.

Statistical analysis of the data was performed using Statistica 10 software. Distribution of the studied quantitative values was described as mean and standard deviation ($M \pm SD$), median, upper and lower quartiles ($Me [Q_1; Q_3]$), as well as limits of 95 % confidence interval. Assessment of correlation between events was performed using Spearman's rank correlation test (R_s). Distribution of categorical values is presented as percentages. For intergroup comparison of qualitative characteristics, two-sided Fisher's exact test was used (p_{TFE}), for numerical data Mann–Whitney U test was used (p_U). Differences were considered significant at $p < 0.05$.

RESULTS

Primary endpoint. In 87 (92.6 %) of 94 cases transplant preservation was observed for the whole follow-up period, in 7 (7.4 %) cases implant was removed. Follow-up period varied between 12 and 64 months, mean follow-up period was 36.3 ± 16.7 months. Six out of 7 complications leading to implant removal developed during first 6 months after operation, 1 complication 14 months after the surgery. In 4 cases, the implant was removed due to postoperative scar dehiscence or trophic disturbances of the flap with implant exposure (at 2, 3, 6 and 14 months); in 2 cases due to infections at the area of surgical intervention at 6 months after the intervention, and in 1 case due to a complication (ischemic acute cerebrovascular event (ACVE)) in the early postoperative period.

Secondary endpoints. Total number of men and women in the study group was equitable, and men were significantly ($p_{TFE} = 0.000018$) younger than women. This circumstance is caused by patient distribution per the cause of cranial defect which also significantly differed between the groups ($p_{TFE} = 0.000001$). Among men, the main cause was brain injury: 46 (86.8 %) of 53 cases, while in dominated craniectomies performed due to resection of benign brain tumors were more prevalent: 20 (48.7 %) of 41 cases, consequences of brain injury amounted to 24.4 %.

In terms of defect area, extensive and giant defects were the most common together comprising 78 (82.9 %) of 94 cases. Per defect size, male and female subgroups did not differ: in men defects with area $>60 \text{ cm}^2$ were observed in 86.8 % of cases, in women in 78 %.

Operative time varied between 25 and 300 minutes (mean 107.4 ± 52.3 minutes) and correlated with defect area ($R_s = 0.47$; $p < 0.05$); correlation was more pronounced with blood loss volume ($R_s = 0.71$; $p < 0.05$).

Blood loss volume varied between 20 and 800 mL with mean value of 175.6 ± 126.9 mL. As noted above, the closest correlation was observed between blood loss volume and operative time, with defect area correlation was weaker ($R_s = 0.43$; $p < 0.05$).

The number of inpatient bed-days varied between 4 and 95 with mean value of 12.1 ± 11.9 . The closest correlation was observed with operative time ($R_s = 0.46$; $p < 0.05$). Other correlations, namely between inpatient bed-days and defect area and blood loss volume, were less pronounced.

Type and number of complications. In total, 12 (12.7 %) cases of complications were observed in the study group, among them 5 (5.3 %) cases occurred during inpatient stay, 7 (7.4 %) during outpatient observation. As stated above, implant removal due to complications was necessary in 7 cases. One removal was performed at day 2 after cranioplasty due to ischemic ACVE in the left middle cerebral artery circulation (on the side of existing defect) and dislocation syndrome; inpatient stay for this patient was 95 days. Other surgical interventions for implant removal were performed 2 and more months after cranioplasty due to complications during outpatient observation. In 1 case of 51-year-old female patient, 6 months after cranioplasty the postoperative scar disruption with implant exposure on the area of up to 0.3 cm^2 was observed. A decision was made not to remove the implant due to the absence of discharge and negative culture test and perform plastic surgery of the formed fistula with local tissues. After the performed operative intervention, repeat complications were not observed, follow-up after surgery was 14 months. In 1 case, complication (coronavirus infection) was not associated with the type of operative intervention. Therefore, the number of purely surgical complications was 11 (11.7 %). Additionally to the stated above, 1 (1.06 %) case each of intracerebral hemorrhage, transudate accumulation (volume 70 mL) under the implant, superficial necrosis of a part of the cutaneous flap were observed. The highest number of complications was observed in patients with giant defects – 7 (7.5 %) cases, for extensive and large defects complications were observed in 3 (3.2 %) and 1 (1.1 %) case, respectively. No deaths were observed after the operative interventions.

DISCUSSION

The question of performing cranioplasty for small defects in the absence of any clinical manifestations remains open while for defects of other sizes the majority of authors support the necessity of surgical intervention [14–16].

In favor of cranioplasty not only for brain protection and improvement of esthetic defects are studies demonstrating improved cerebrospinal fluid circulation, normalization of intracranial and cerebral perfusion pressure and improved cognitive function after the surgery [17–22].

Individualized titanium implants manufactured by 3D printing has been used in Russian neurosurgical practice since 2016 [23]. In our study, we evaluated long-term outcomes of cranioplasties using these devices in one clinical center.

Mean defect area in the study group corresponded to extensive defects, and this pattern was observed both in men and women. Analysis of quartile distribution showed that in men the lower quartile value was 89.1 cm^2 , upper quartile was 126.6 cm^2 ; in women, lower and upper quartiles were 61.8 and 120.8 cm^2 , respectively. These characteristics are reasonable: among men most patients had craniotomies due to brain injury for which adequate decompression volume is the main goal of surgical intervention [24].

The primary endpoint of the study was implant survival for a period of at least 12 months after the surgery, and in accordance with this condition 87 (92.6 %) clinical observations demonstrated preservation of the implant. The dominating cause of implant removal ($n = 4$) was development of trophic disturbances of the cutaneous aponeurotic flap with postoperative scar dehiscence and implant exposure, mostly between months 2 and 6 after discharge from the hospital. The 2nd most common cause of implant removal was infections in the area of surgical intervention ($n = 2$) which developed without skin penetration and manifested through typical symptoms: fever, hyperemia, local edema and pain.

Implant exposure due to trophic disturbances of the cutaneous aponeurotic flap and postoperative scar dehiscence is a significant complication leading, as a rule, to implant removal with incidence, according to the literature, of about 14 % of cranioplasties using titanium implants [25]. For example, in the study by T. Maqbool et al. (2018) [26] this complication was observed in 14 % of patients, and significant predictors for titanium implant exposure were radiotherapy prior to cranioplasty (odds ratio (OR) 19.67, $p = 0.018$), plastic surgery with distant flap (OR 6.50, $p = 0.046$), atrophy of the soft tissues of the head (OR 10.71, $p = 0.040$). The authors note that radiotherapy performed after cranioplasty, transposition of the cutaneous aponeurotic flap, free epidural space under the implant are not significant causes of implant exposure, but in some cases this complication can develop in the context of these conditions. A. Thien et al. (2015) [27] observed titanium implant exposure requiring repeat reconstructive interventions in 13.9 % of cases. In our case series, significant predictors for implant exposure were not identified. Based on surgical experience, the most probable cause of wound dehiscence is flap tension during wound suture developed due to 2 factors: on one hand, due to skin constriction in the context of defect persistence, on the other hand due to large area implants with curvature corresponding to the lost bone.

C. Morselli et al. (2019) [28] performed systematic literature review on the use of various materials for cranioplasty. They showed that incidence of infections complications in the group of titanium implants was 10.17 %, in 7.7 % of cases conservative treatment was ineffective, and implant removal surgery was necessary.

Results of systemic review of using various types of implants for cranioplasty by J.D. Oliver et al. (2019) which included data from 3,591 adult patients, show 6.02 % of infectious complications in the titanium implant group; local complications (including hematomas, screw failure, implant fracture, postoperative scar dehiscence, implant exposure) in this group were observed in 13.09 % of cases; implant removal was performed in 6.02 % of cases [29].

The study by S.A. Chobulov showed 2 (2.2 %) cases of infectious complications in the group of 92 patients who underwent cranioplasty using titanium implants, and 3 (6.1 %) cases of infections in the group of 49 patients who received implants made of titanium mesh with polymethylmethacrylate [13].

The use of 3D printing for direct manufacturing of individualized implants has a number of benefits: it does not require manufacturing of interim items – anatomical models and press forms, it allows to design various non-standard elements, for example, openings for under-implant space drainage or suturing of the temporal muscle to the plate, reinforcement ribs, changes in geometry of the mesh structure. Additionally, due to preparatory 3D modeling, changes in the curvature and geometry of the implant are possible to reduce esthetic defect developed due to temporal muscle atrophy on the surgery side.

CONCLUSION

In our case series, incidence and type of complications did not contradict the existing international and Russian literature. Total number of complications was 12 (12.7 %), among them 11 (11.7 %) were associated with surgical treatment. The most common complications were postoperative scar dehiscence and trophic disturbances of the cutaneous aponeurotic flap – 5 (5.3 %) cases which led to titanium implant exposure, and in 4 cases caused plate removal. The 2nd most common complications were infections – 2 (2.1 %) cases leading to implant removal. Other complications, such as ACVE in the early postoperative period, intracranial hemorrhage, necrosis of a part of the cutaneous aponeurotic flap were observed in 1 patient each. Liquid accumulation under the implant was observed in 1 of 94 observations. Data on complications after cranioplasties vary between studies, and results of reconstructive interventions using individualized titanium implants which became more common in the last 5 years due to implementation of additive medical manufacturing is of special interest.

Therefore, we have obtained the following results:

- in 87 (92.6 %) of 94 observations preservation of individualized titanium implant was observed for the full follow-up period; in 7 (7.4 %) cases the implant was removed;
- the most common causes of implant removal were exposure of the individualized titanium plate (4 (4.3 %) cases) and infection of the area of surgical intervention (2 (2.1 %) cases);
- most commonly, complications leading to implant removal developed in the first 6 months after surgical intervention.

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Authors' contributions

S.V. Mishinov: research design development, obtaining data for analysis, data analysis, statistical analysis, article writing, surgical treatment, patient supervision;

N.A. Koporushko: obtaining data for analysis, surgical treatment, patient supervision;

V.V. Stupak: scientific editing of the article.

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Compliance with patient rights and principles of bioethics.

The study protocol was approved by the biomedical Ethics Committee of the Ya.L. Tsivyan Novosibirsk Research Institute of Traumatology and Orthopedics of the Ministry of Health of Russia. All patients gave written informed consent to participate in the study.