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The efficacy of using the allogeneic osteoplastic material in skull trepanation

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Abstract

Introduction. *When performing osteoplastic craniotomy, there is a need to fill the diastasis between the skull bone and the explanted bone fragment. Grafts based on allogeneic bone chips and collagen (bone-plastic material) may be very effective for cranial bone repair in diastasis area.*

Aim. *To evaluate the safety and clinical efficacy of osteoplastic material during the osteoplastic craniotomy.*

Material and methods. *A retrospective and prospective clinical study was conducted at the N.V. Sklifosovsky Research Institute for Emergency Medicine and included 12 patients treated in Urgent Neurosurgery*

Department with diagnoses suggesting the need for craniotomy. Allogenic osteoplastic material was obtained from a 0.7-0.9% solution of type I collagen and spongy bone chips with a fraction size of 315-630 microns. Osteoplastic material grafts were used intraoperatively at the cranioplastic stage of the operation after the main stages had been completed. The efficacy and safety of the use of osteoplastic material were evaluated clinically and radiologically in the early postoperative period.

Results. *In the early postoperative period, the study patients had no pyo-septic complications, severe pain or soft tissue swelling. All patients were discharged from the hospital in satisfactory condition to be followed-up by the physician or neurologist at the out-patient facility. The computed tomography performed in the early postoperative period visualized the diastasis lines along the bone flap line in the comparison group patients (without osteoplastic material); and in the main group, the osteoplastic material was clearly visualized. At computed tomography of the skull performed after 6–9 months and after 2–18 months, the signs of bone tissue consolidation were visualized in the patients of the main group. The radiodensity of the autologous bone flap in both groups did not significantly change at any periods. In the diastasis area, the radiodensity of diastasis in the main group was significantly higher than in the comparison group. After 1-1.15 years the radiodensity values in the diastasis area increased by average of 1.95 times ($p<0.05$) in the patients of the main group, while in the patients without osteoplastic material, this parameter did not significantly change during the entire follow-up period.*

Conclusions. *In patients with intraoperative cranioplasty osteoplastic material grafts did not cause complications in the early and late postoperative period. Intraoperative cranioplasty performed with using osteoplastic allogeneic material caused no complications in either early or* *late postoperative periods. The presence of osteoplastic material contributed to the consolidation of the autologous bone flap and healthy bone.*

Keywords: *osteoplastic* material, diastases, radiodensity, bone consolidation

Conflict of interests Authors declare no conflict of interest

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BMP, bone morphogenetic protein
CT, computed tomography
ICD, International Classification of Diseases
OPM, osteoplastic materials
ROI, region of interest

Introduction

When performing craniotomy using a craniotome, bone defects are formed in the area of surgical access in the form of burr holes and diastasis between the skull and the sawed bone fragment [1, 2]. The presence of diastases prevents the formation of bone callus, creates a risk of developing adhesions, and can lead to disruption of hemo- and liquor circulation, and to bone tissue lysis [3–5]. Calvarium represented predominantly by the plates of compact bone substance has a low ability to regenerate [1, 4]. So, restoring the integrity of the cranial dome after trepanation requires additional stimulation of reparative and regenerative processes.

Bone consolidation depends on the following aspects: tight fit of bone fragments, their immobility and degree of juxtaposition, effective blood supply to the fracture area. One of the ways to stimulate osteogenesis is the use of osteoplastic material (OMP) containing allogeneic fine bone fragments, namely bone chips containing bone morphogenetic protein (BMP) and human type I collagen [6, 7]. Collagen has been shown to have a reparative effect, primarily due to its high conductivity (the ability to stimulate cell migration). Bone chips have osteogenic and osteoinductive properties and are widely used in related areas of clinical practice. Methods for the production of OPM based on collagen and bone chips are currently being developed. Bio-Oss and Inter-Oss products manufactured by using cattle tissue are widely known [8]. According to researchers, Bio-Oss and Inter-Oss materials stimulate bone regeneration and cause no marked inflammatory and immunological complications in experiments [8, 9]. However, for practical use, OPMs made from human tissue are more attractive, since allogeneic materials have potentially lower immunogenicity compared to xenogeneic ones. To date, there is no data on the efficacy of such OPM in clinical practice in the treatment of calvarial defects.

The objective was to evaluate the safety and clinical efficacy of osteoplastic material based on allogeneic type I collagen and allogeneic bone chips during osteoplastic craniotomy.

Material and methods

A retrospective and prospective clinical study conducted in 2021–2023 at the N.V. Sklifosovsky Research Institute for Emergency Medicine included 12 patients (2 men, 10 women) aged from 25 to 69 years treated in the Urgent Neurosurgery Department who underwent osteoplastic craniotomy (I67.1; I60.2; Q28.0 in ICD-10). The clinical pattern after the trepanation with using OPM was assessed as part of a prospective study, without using OPM in a retrospective study.

The patients were divided into two groups depending on the use of OPM during surgery: the main group included 7 patients in whom the cranioplastic stage of surgery was performed using OPM, the comparison group consisted of 5 individuals in whom the cranioplastic stage of surgery was performed without OPM. Patients in the main group and the comparison group were comparable in terms of gender and age characteristics, severity of pathology, and the volume of trepanation performed (Table).

Table. Characteristics of the studied patients with craniotomy

Compared parameters	Main group (treatment with OPM)	Comparison group (treatment without OPM)
Gender ratio	6 women/1 men	4 women/1 man
Underlying disease (ICD-10 code; number of patients)	I67.1; 4 Q28.0; 2 I60.2; 1	I67.1; 4 I60.2; 1
Age, years	41 (40;65)	44 (30;61)
Explanted flap area, cm^2	42 (40;49)	40 (38;45)

Note: ICD-10 – international classification of diseases

The study was conducted in accordance with ethical standards and approved by the decision of the Local Ethics Committee (Protocol No. 3-19 of August 19, 2019). The patients' consent to participate in the study was previously obtained in written and oral forms.

Before surgery, all patients were examined according to a standard procedure and extent using laboratory and instrumental diagnostic techniques (electrocardiography, computed tomography of the brain, angiography, Doppler ultrasound of the lower limb veins, chest photofluorography, clinical blood tests and urinanalysis, coagulogram, blood biochemistry).

Manufacture of osteoplastic material

Osteoplastic material for filling bone tissue defects was developed at the N.V. Sklifosovsky Research Institute for Emergency Medicine. OPM was obtained from a 0.7–0.9% solution of allogeneic type I collagen and allogeneic spongy bone chips with a fraction size of 315–630 μm. A solution of human type 1 collagen was isolated from the tendons of tissue donors by acid extraction in 0.01 M acetic acid, bone chips were obtained from the cancellous bone of tissue donors by crushing and sieving through a filter. The collagen solution was mixed with bone chips until a homogeneous mass was obtained, after which 100.0 ml of the resulting mixture was evenly distributed over a 10x10 cm Petri dish (Fig. 1A). The finished mixture was placed in a VirTis freeze-ultra 2.0 drying chamber (USA). Lyophilization was carried out under vacuum with cooling to -35°C for 30 minutes; later on, the temperature was gradually raised to +36°C over 24 hours. Lyophilized OPM was cut into pieces of 5 to 10 cm^2 in an area (Fig. 1B) and placed in double polypropylene bags using an electric vacuum sealer. Sterilization of the OPM was achieved by irradiation treatment with a dose of 25 kGy. The sterility control was ensured in the Microbiological Laboratory of the Institute. The finished sterilized OPM samples were stored at room temperature. From the moment the OPM was prepared until it was used in the clinic, 3–6 months passed.

Fig. 1. The view of mixed osteoplastic material in a Petri dish before lyophilization (A) and after lyophilization (B)

Surgical technique

Osteoplastic material was used after completion of the main stage of surgery while applying and fixing the bone flap. After removal from the sterile packaging, the OPM was placed in sterile distilled water immediately before use to achieve neutral pH values. The exposure lasted for 30 minutes.

Using tweezers and a spatula, the required OPM portion was tightly placed into the bur holes and along the perimeter of the bone fragment, which made it possible to almost completely fill all the resulting bone clefts (Fig. 2). The bone flap was fixed with titanium plates and microscrews.

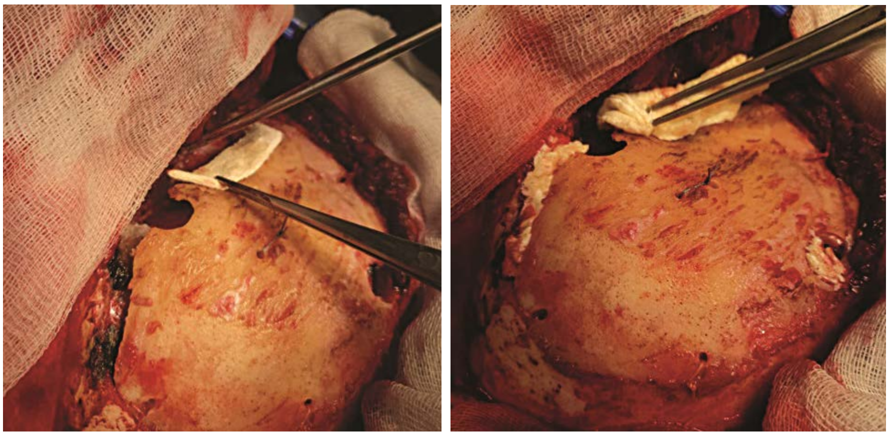

Fig. 2. Intraoperative photo. Filling bone defects with osteoplastic material

Methods for assessing results

The efficacy and safety of the OPM use was assessed at clinical tests and radiological examinations in the early postoperative period (within the 1st week after cranioplasty). The condition of the skin around the post-surgery suture, the presence of hyperemia, edema and wound discharge were assessed. Computed tomography (CT) of the skull was performed in the first week after surgery, after 6–9 months, and after 12–

18 months to assess the bone tissue consolidation, the bone flap condition, and the OPM distribution. CT was performed without a contrast with a slice thickness of 0.5–1 mm, in the bone window WL 1000/ WW 3000. Bone density was measured by a round ROI (region of interest) with a diameter corresponding to the thickness of the bone in the contralateral area (healthy bone located symmetrically from the defect area) without involving soft tissue areas and cerebrospinal fluid space. The radiodensity of healthy bone, autologous bone flap, and diastasis area was assessed. To assess the bone tissue integrity in the autologous flap and bone regeneration in the area of diastasis, the density coefficient was calculated by the formula $K = D_{defect} / D_{native} \times 100$, where D_{defect} is the mean radiodensity of bone in the defect area, D_{native} is the mean radiodensity of native bone located symmetrically (bone tissue in the contralateral area). Density coefficient K was calculated to assess the safety of the autologous bone flap (K1) and assess bone restoration in the area of diastasis (K2).

Statistical processing

Statistical analysis was performed using the “Statistics” software package for Windows 11 (Microsoft, USA). The median (Me), 1st and 3rd quartiles (1Q;3Q) were calculated. The Mann–Whitney test was used to compare the data between groups. Differences were considered statistically significant at a significance level of more than 95% ($p<0.05$).

Results

The early and late postoperative period in both groups proceeded identically; no pyo-inflammatory complications were detected in any patient of the compared groups. In the early postoperative period, on days 2–3, in both groups there was slight hyperemia in the suture area, which was associated with the surgical intervention. Postoperative swelling of soft tissues in the wound area persisted in both groups for 3–5 days. All patients were discharged from the hospital in satisfactory condition to be followed-up by the physician or neurologist at the out-patient facility. Thus, the use of OPM caused no adverse reactions or side effects in the early postoperative period.

In the patients of the main group, in the early postoperative period, along the bonesaw-line, and along the perimeter of the bone flap placed in site, the OPM was visualized, the burr holes were also filled with it, and the OPM elements were noted under the bone flap along the course of the dura mater. When assessing the computed tomography of patients in the comparison group (without OPM) at that time, the diastasis of 1.0–3.0 mm wide was visualized along the boundaries of the bone flap as well as the area of the burr holes.

At 6–9 months after surgery, in 6 of 7 patients of the main group and in 3 of 5 patients of the comparison group, the CT scanning of the skull showed the signs of consolidation in the form of local bone bridges appearing between the flap and the bonesaw-line of the native bone. In addition, in the main group, additional zones of consolidation were identified in patients in the areas of diastasis filled with OPM (Fig. 3).

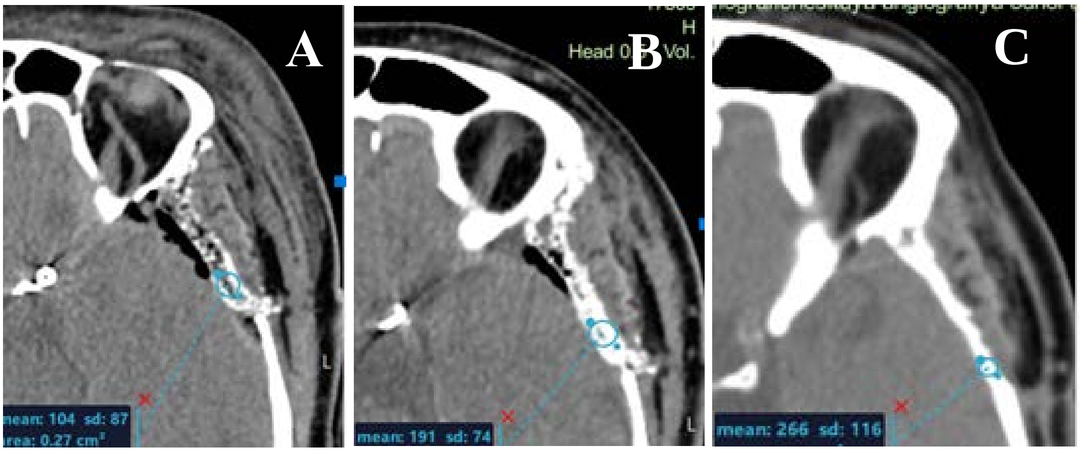

Fig. 3. Computer tomogram of the skull in the axial plane after osteoplastic craniotomy in the left frontotemporal region using osteoplastic material: A, on day 1; B, after 1 week; C, at 6 months after surgery. There is a gradual increase in the bone radiodensity of the OPM in the area of the defect: on day 1, the radiodensity was 104 HU (the OPM radiodensity values of the are distorted by gas inclusions); after 7 days the radiodensity was 191 HU (the gas content decreased); after 6 months there was OPM compaction with an increase in density up to 266 HU

After 12 months, in all patients of both groups, when examined in the defect area, there were no signs of the development of complications, such as an inflammatory process, separation of cerebrospinal fluid and pus, or melting of adjacent soft tissues. The skin in the area of surgical intervention had a normal structure, the hairline was not disturbed. Upon palpation, the operated area did not differ from the surrounding bones of the skull; symmetry was preserved in all cases. According to CT data, in patients of the main group there were areas of marginal osteogenesis with a progressive decrease in diastasis between the flap and the edge of the bonesaw-line, up to complete consolidation in certain areas, there were signs of the appearance of areas of calcification along the course of the dura mater, a more uniform nature of consolidation was noted along the perimeter of the flap than in patients from the comparison group (Fig. 4).

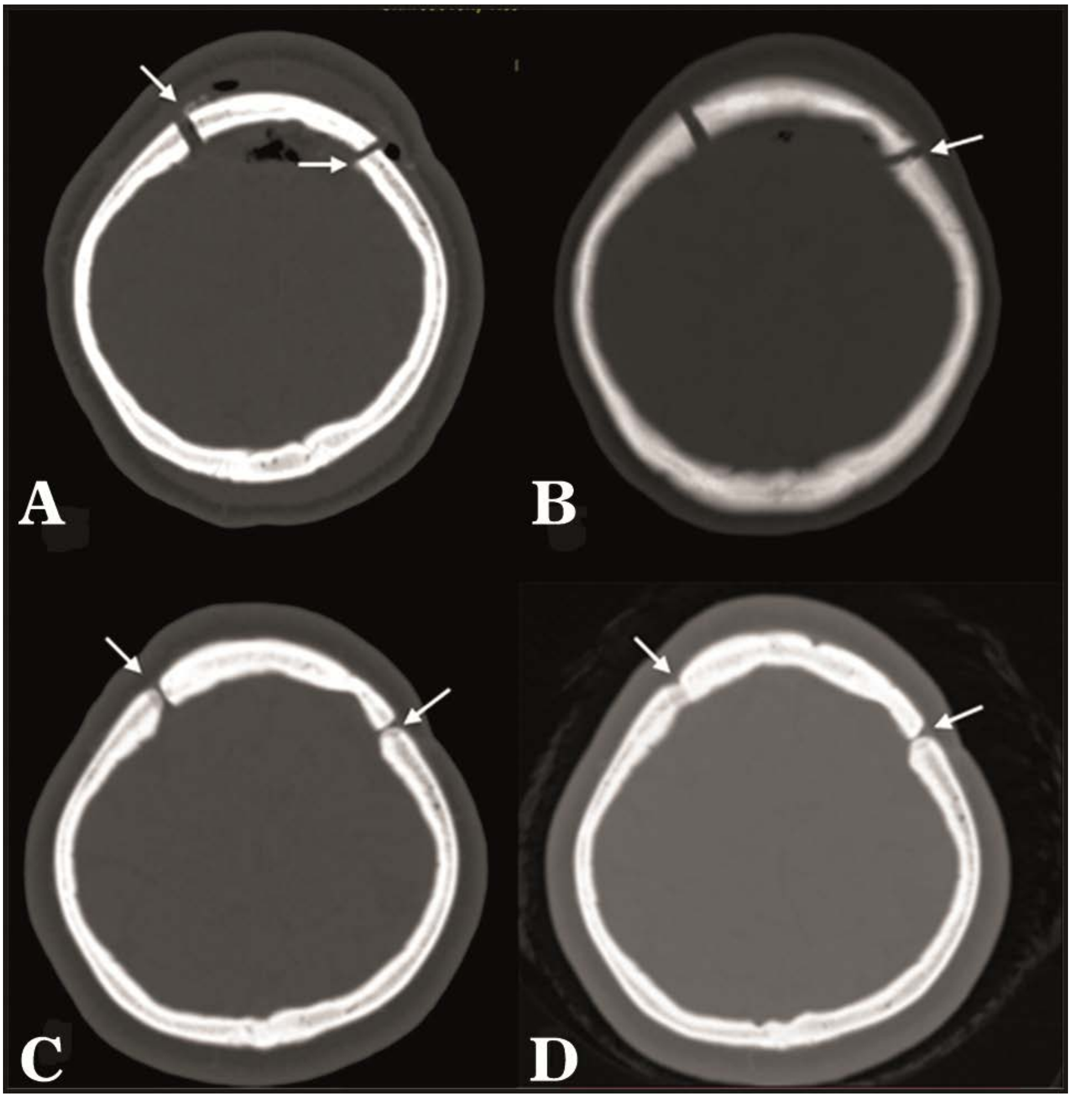

Fig. 4. Computed tomography of the skull in the axial plane after osteoplastic craniotomy in the frontal region with using osteoplastic material: A, 1 week after surgery: OPM can be traced along the edges of the positioned bone flap (arrows), with postoperative gas inclusions; B, 3 months after surgery: the edges of the bone flap and bonesaw-line retain the same configuration, initial signs of osteogenesis are noted in the form of an appearing spike-shaped area of newly formed bone tissue along the edge of the bonesaw-line (arrow); C, 6 months after surgery: arrows show the appearance of newly formed bone tissue along the edges of the flap and bonesaw-line with rounding of their contours and a decrease in diastasis; D, 15 months after surgery: ongoing osteogenesis with a decrease in diastasis (right) and an area of complete consolidation (left)

The exception was 1 patient, who showed the signs of consolidation and marginal osteolysis of the flap simultaneously. In the area of osteolysis, the thinning of the bone flap, an increase in diastasis between the flap and the edge of the native bone in some areas, and the presence of cortical defects were observed (Fig. 5, 6).

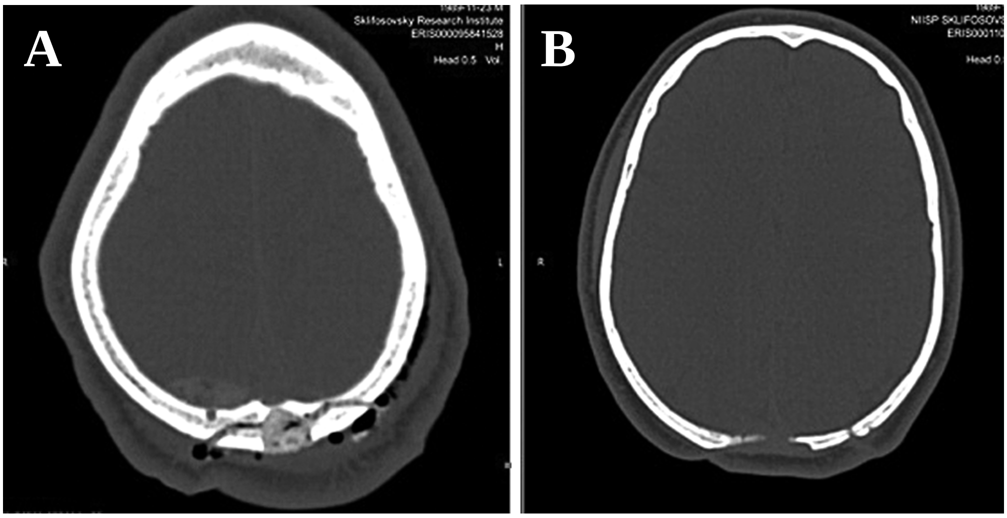

Fig. 5. Identifying the signs of autologous flap osteolysis osteolysis after osteoplastic craniotomy. Computed tomography image of the skull in the axial plane: A, 1 day after surgery; B, after 12 months. After 12 months, an area of marginal osteolysis of the bone flap is visible in the area of the burr hole, initially filled with OPM; there are signs of OPM lysis in the area of plastic surgery

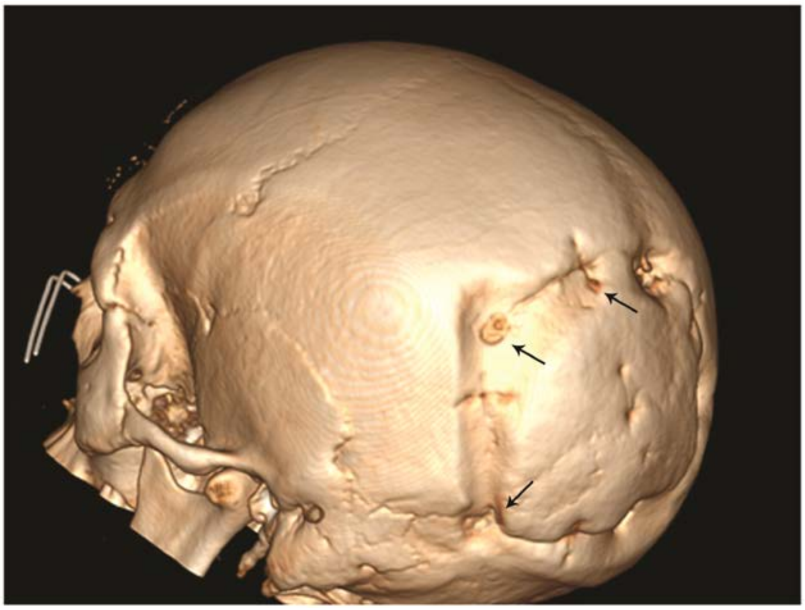

Fig. 6. Reconstruction of the skull with the signs of autologous flap osteolysis using volume rendering technique (VRT): against the background of the bone flap consolidation, the areas of edge osteolysis are visible at the sites of the burr holes (shown by arrows) with thinning of the bone flap along the periphery

Signs of the bone flap cancellous substance restructuring with the appearance of cyst-like structures in it were noted in 2 patients. One of them was the described above patient of the main group with the signs of osteolysis of the bone flap. In the patient from the comparison group, despite the absence of statistically significant osteolysis signs in the compact substance of the flap, its density was reduced due to the presence of cyst-like areas of bone tissue rarefaction (Fig. 7).

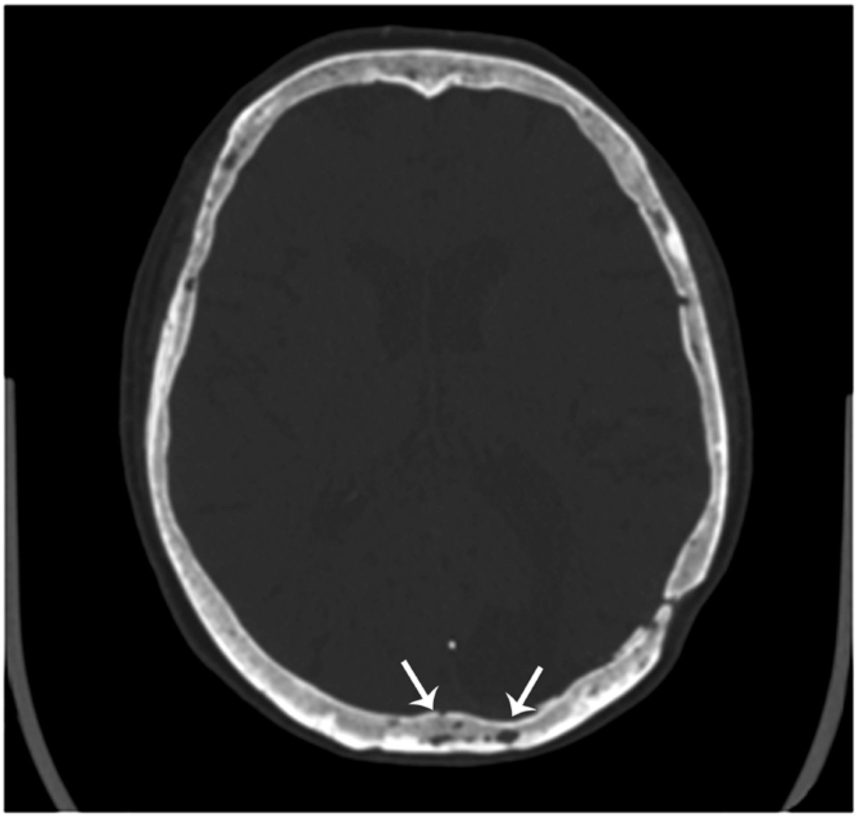

Fig. 7. Identification of areas of geode restructuring of the autologous flap in a patient at 12 months after osteoplastic craniotomy (shown by arrows). Computed tomography image of the skull in the axial plane. Areas of geode restructuring are revealed against the background of flap consolidation without edge osteolysis and without the presence of endplate defects

With the exception of the two patients described above (Fig. 5–7), the radiodensity of the autologous bone flap in both groups underwent no visible changes at any follow-up periods. This indicated the preservation of the autograft general structure, the absence of its decalcification and pronounced degradation of the matrix.

At the same time, in the area of diastasis, the radiodensity value and K2 coefficient in the main group was statistically significantly higher than in the comparison group (Table 2). After 1–1.15 years, in patients of the main group, K2 increased at mean by 1.95 times compared to the value 1 week after surgery ($p < 0.05$). On the contrary, in patients without OPM, the K2 did not change significantly throughout the entire follow-up period. Thus, the presence of OPM in the diastasis promoted the growth of bone tissue in the diastasis area. Moreover, after 1–1.5 years, the consolidation of the autologous flap bone tissue with the healthy bone was not completed in the patients.

Table 2. Radiodensity values in patients with and without the use of osteoplastic material at various periods of follow-up

Radiodensity, HU	Patients with OPM Me (1Q;3Q)		Patients without OPM Me (1Q;3Q)	
	After 1 week	After 1–1.5 years	After 1 week	After 1–1.5 years
Bone flap in the trepanation area	1342 (1171;1470)	1377 (1268;1434)	1453 (1184;1438)	1290 (1160;1450)
Bone tissue in the contralateral area	1325 (1170;1450)	1348 (1180;1406)	1467 (1130;1640)	1304 (1188;1454)
In the area of diastasis	258 (138;407)	502 (192;623)$^{+}$	67 (50;75)*	57 (52;77)*
K1 coefficient	1.01	1.02	0.99	0.99
K2 coefficient	0.19	0.37^{+}	0.04*	0.04*

Notes: * statistically significant relative to patients with osteoplastic material at the same stage of analysis $p<0.05$; $^{+}$ statistically significant relative to the values after 1 week $p<0.05$.

Discussion

The process of restoring the functional state and the architecture of bone tissue after massive injury is an important task in regenerative medicine [1–4, 10]. Experimental models have shown a high ability of grafts based on collagen and bone components to stimulate osteogenesis and integration into a healthy cancellous bone [11–14]. It is worth noting that the osteogeneic effect of different OPM types described in the literature was noted mainly in tissues with a high vascular density and the ability to active angiogenesis, both in models in vivo, and in clinical use of OPM [8, 9, 13, 14]. Repair of cortical bone using collagen-bone bioconstructs and grafts has been studied to a much lesser extent. Many authors have noted that in a clinical setting, cranioplasty using any type of grafts based on biological tissues or polymers has great difficulties [2 – 5]. This is largely due to the structure of the cranial dome bones. In the cortical layers of the bone, the possibility of vascular migration of cells is noticeably reduced, which creates the need to increase biological conductivity in the bone flap area [15]. For this purpose, highly adhesive components, growth factors, and angiogenic factors can be used as part of various biological constructs and grafts [16–18]. The efficacy of such products has been demonstrated by the examples of experimental models in vivo, however, these products have not yet found widespread use in clinical practice due to the complexity of their manufacture and insufficient standardization. Currently, grafts based on hydroxyapatite (the main mineral component of bone) are widely used in cranioplasty. Hydroxyapatite products can have different shapes, are non-toxic and have osteogenic potential [19]. Hydroxyapatite-based grafts are obtained both artificially and by using bone tissue from tissue donors, therefore, in a number of literature report, the granulated hydroxyapatite grafts and bone chips are considered as identical products [6, 8–10]. The efficacy of osseointegration when using hydroxyapatite grafts is estimated by different researchers to be from 80 to 95% [19, 20]. There is an opinion that for effective cranioplasty it is necessary to completely replace the bone flap with a hydroxyapatite-based implant [20]. However, this approach requires a high-level material resources and technological equipment. In addition, when working with hydroxyapatite grafts, bone cement is used to fill diastases, which prevents an active cell migration and vascular growth. On the contrary, OPM based on collagen and bone chips consists of biodegradable materials, is adhesive to human cells, and can be additionally saturated with growth factors and other biologically active substances [7]. In this study, we did not use additional biological agents to stimulate osteoconductive and osteogenic processes. However, in the OPM treatment group, 6 of 7 patients showed a timely occurred clinical and radiological fusion of the bone flap with the native skull bone, which indicated the effective integration of OPM and stimulation of osteogenesis. OPM based on allogeneic materials caused neither pyo-inflammatory complications nor adverse side effects. We believe that OPM grafts manufactured up to our proposed method [7] can potentially be used both in cranioplasty, and also in the treatment of other bone tissue defects.

Conclusion

The study showed the prospects of using the osteoplastic material we had developed based on allogeneic materials to eliminate defects of the cranial dome, which can be a good alternative to the use of synthetic or xenogeneic materials. The limitation of our study is the small number of patients, so further research in this area is required, including the assessment of the autologous flap and the diastasis zone at a stage of 2 years or more from the date of surgery, determining the time of complete fusion of the autologous flap with the healthy bone, assessing the impact of individual patient characteristics during restoration of the cranial dome when using osteoplastic material.

Based on our study results we can make the following conclusions:

- The use of osteoplastic material during craniotomy in patients is safe and leads to no development of complications in either early or late postoperative periods.
- In patients who were treated with using osteoplastic material, the relative radiodensity in the area of diastasis increased by 3.9 times 1 week after surgery and by 8.9 times 1–1.5 years after operations as compared to the patients in the comparison group.
- The use of osteoplastic material stimulated bone regeneration in the area of diastasis. The relative radiodensity in the area of diastasis in the patients in whom osteoplastic material was used increased by mean of 1.95 times after 1–1.15 years compared to the values at 7–10 days after surgery.
- The presence of osteoplastic material in the diastasis contributed to the consolidation of the autologous bone flap and the healthy bone at 6–18 months after surgery.

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