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Original Article

Neurocognitive outcome post cranioplasty: The role of cerebral hemodynamics and cerebrospinal fluid dynamics

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ABSTRACT

Background: Cranioplasty has been useful in treating the symptoms associated with the "Sunken skin flap syndrome" post decompressive craniectomy, for which various mechanisms have been proposed. In this study, we aim to assess the changes in the cerebral blood flow and intracranial cerebrospinal fluid (CSF) dynamics post cranioplasty and correlate with the improvement in the neurocognitive status.

Methods: Computed tomography perfusion and cine magnetic resonance imaging studies were done to study the changes in cerebral perfusion and CSF flow dynamics postcranioplasty. The cognitive status was assessed using Montreal cognitive assessment, mini-mental state examination, and frontal assessment battery scores in the preoperative period and at 1 and 6 months follow-up.

Results: There was a significant change in cognitive status postcranioplasty, both at 1 and 6 months follow-up, which was associated with a significant improvement in cerebral blood flow, decreased mean transit time, and improvement in the mean and peak CSF flow velocities at the foramen of Magendie and aqueduct of Sylvius.

Conclusion: Cranioplasty leads to a marked improvement in cerebral hemodynamics, which is more significant on the ipsilateral side. It also leads to increased CSF turnover and improved CSF circulation. Improved cerebral perfusion and, more importantly, CSF dynamics may be responsible for the demonstrable improvement in the neurocognition in the postcranioplasty period.

Keywords: Cerebral hemodynamics, Cerebrospinal fluid flow, Computed tomography perfusion, Cranioplasty, Neurocognition

INTRODUCTION

Decompressive craniectomy (DC) is a lifesaving procedure to treat medically refractory intracranial hypertension in patients with severe head injury.^[32] Even though DC is effective in reducing refractory elevation of intracranial pressure as well as mortality rates, it has resulted in a concomitant increase in morbidity, vegetative states, and severe disability rates.^[4,18] Post-craniectomy patients are prone to numerous complications such as post-traumatic hydrocephalus, subdural hygroma, seizures, hemorrhage, infection, cerebrospinal fluid (CSF) leakage, and the bony defect, in itself, maybe a symptom.^[2] The term "syndrome of the trephined" was defined^[15] to refer to the cluster of symptoms associated with a bony defect, including dizziness, undue fatigability, vague discomfort

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at the site of the defect, mental depression, and intolerance to vibration which resolves after bone replacement. Yamaura and Makino, Yamaura *et al.*,^[36,37] coined the term"sinking skin flap syndrome (SSFS)" to describe a similar constellation of reversible symptoms in postcraniectomy patients, which improved after bone flap replacement.

The "sinking" of the skin flap due to atmospheric pressure onto the dura with irritation of the cortical tissue and gliosis ^[9,33] may provide a mechanical explanation for the symptoms. Segal et al.^[28] hypothesized the presence of cortical scar tissue compressing the underlying cortex and sub-arachnoid space, which, along with the atmospheric pressure, could alter the cerebral hemodynamics. Richaud et al.[26] observed significant improvement in the cerebral blood flow (CBF) in the region of the previous bony defect which correlated with the neurological improvement after cranioplasty. Dujovny et al.^[10] described an increase in CSF motion after cranioplasty in a single index case using the phase contrast (PC) magnetic resonance imaging (MRI) technique. More recently, Panwar et al.^[24] demonstrated an improvement in CSF flow post cranioplasty, showing a positive correlation with improvement in neurocognitive status. Another recent interesting hypothesis by Plog et al.^[25] is the post-craniectomy impairment in the glymphatic flow produced by impaired arterial pulsations, which were demonstrated to produce neurological deficits in murine models.

The neurological recovery after cranioplasty is multifactorial, and this study aims to investigate the impact of changes in CSF dynamics along with cerebral blood flow on improvement in neurocognitive outcomes in post-cranioplasty patients.

MATERIALS AND METHODS

We performed a prospective observational single-center study on 26 consecutive patients who were operated on in the Department of Neurosurgery, SMS Medical College and Hospital for cranioplasty post-head injury between September 2017 and August 2019 after clearance from the Institutional Ethical Committee. Patients with previous CSF diversion surgery, repeated head injury, previous history of cognitive impairment or mental retardation, and allergy to iodine contrast were excluded from the study. Written and informed consent was obtained from the patient and/or nearest relative.

Cine phase retrospective cardiac gated MRI to assess CSF flow at the aqueduct of Sylvius and foramen of Magendie was done. Computed tomography perfusion (CTP) study brain was obtained to assess the baseline cerebrovascular hemodynamic parameters. Both the CTP and Cine MRI studies were repeated on the 7th postoperative day and the results were compared with the preoperative study.

Neurocognitive assessment of all the enrolled patients was done using the Montreal cognitive assessment (MoCA)

score, mini-mental state examination (MMSE) score, and frontal assessment battery (FAB) preoperatively.^[8,14,23] The examinations were repeated at 1 and 6-month intervals in the postoperative period and compared with baseline scores to assess the change in neurocognitive function. The neurocognitive improvement in unconscious patients was evaluated with improvement in the Glasgow coma scale (GCS) score.

CTP analysis was performed using a 40-slice computed tomography (CT) scanner (Philips) using a 40-slice long continuous (cine) scan. One hundred and twenty axial images were constructed with eight 5 mm thick sections which covered a total of 40 mm thickness (as per available CT scanner). The CT scanner protocols are 80 kV, 209 mA, 1 s per rotation at 0° gantry. The CTP scan was started with a 4 s delay after the injection of 50 mL non-ionic contrast agent Iopamidol at a rate of 4 mL/s with an infuser pump. Perfusion maps were generated for each patient, and CBF and mean transit time (MTT) were measured in five regions of interest (ROI), that is, orbitofrontal cortex (OFC), internal capsule (IC), thalamus, caudate nucleus, and white fiber tract from Motor-Sensory Cortex (MSC). The ROI was manually drawn in the CTP images both on the same and contralateral side as the craniectomy defect and the values were generated and compared with the help of the manufacturer's software package of CTP.^[24]

CBF is defined as the volume of blood that flows per unit mass per unit of time in brain tissue and is typically expressed in milliliters of blood per minute per 100 g of brain tissue.^[11] MTT^[5] corresponds to the average time, in seconds, that red blood cells (RBCs) spend within a determinate volume of capillary circulation. An increase in CBF corresponds to better perfusion at a given time, and a decrease in MTT shows a reduction in RBC stasis.

Cine MRI study was performed on a 3-T magnetic resonance scanner (Philips) with a 30 mT/m maximum gradient strength and a 150 mT/m per millisecond slow rate using a head coil. The PC velocity encoded cine MRI (TR/ TE:15.0/2.1, FOV: 230, matrix: 512×512 , Voxel size: $0.575 \times 0.575 \times 1$ mm) was obtained using Retrospective Cardiac Gating and 13 phases were evaluated for each cardiac cycle. Subsequent analysis and measurements were carried out using the manufacturer's software package. Peak CSF flow rate and mean CSF velocity were evaluated for each patient at the aqueduct of Sylvius and foramen of Magendie.^[24]

Statistical analysis was done using computer software (Statistical Package for the Social Sciences trial version 24). The qualitative data were expressed in proportion and percentages, and the quantitative data were expressed as mean \pm standard deviations. The difference in proportion was analyzed using the Chi-square test, and the difference in means was analyzed using either two-tailed paired *t*-tests



Figure 1: (a) Box and whisker plot showing improvement in cognitive function using Montreal cognitive assessment scores. (b) Box and whisker plot showing improvement in cognitive function using mini-mental state examination scores. (c) Box and whisker plot showing improvement in cognitive function using frontal assessment battery scores. MoCA: Montreal cognitive assessment score, MMSE: Mini-mental state examination, FAB: Frontal assessment battery.

or the Wilcoxon sign-ranked test, depending on the type of distribution of data determined by the Shapiro–Wilk test. An error probability of <0.05 was considered to be statistically significant.

RESULTS

Twenty-six patients were recruited for the study, and CTP and Cine MRI studies were done for all the patients according to the specified protocol except for one patient who could not undergo Cine MRI due to significant motion artifacts. The change in neurocognitive status post-cranioplasty was evaluated at 1-month and 6-month intervals postcranioplasty, which could not be attained for three patients who were lost to follow-up.

The study population comprised 21 males (80.76%) and five females aged 18–63 years, with a mean age of 32.2 years. All the participants had undergone DC 3–44 months before cranioplasty, with two outliers at 65 and 84 months. The mean time difference between the two surgeries was 16.46 months. At the time of undergoing surgery, 21 out of 26 patients were conscious and cooperative, but five had impaired consciousness, with GCS scores ranging from 4 to 11. The participants had, on average, 9.3 years of formal education, and only 11 subjects had received 12 or more years of education.

The change in neurocognitive status assessed with MoCA, MMSE, and FAB scores all showed significant improvements measured at 1- and 6-month duration postsurgery [Figure 1]. The mean MoCA, MMSE, and FAB scores showed improvement from baseline score to 6-month scores: 12.61–16.36 (P = 0.00), 15.65–19.18 (P = 0.001), and 7.57–9.45 (P = 0.001), respectively [Figure 1]. The change from baseline to 1-month score assessed using MoCA (12.61–12.82), MMSE (15.65–16.21), and FAB (7.57–8.04) was also found to be significant. Among the five patients who were unconscious at the time of surgery, two showed neurologic improvement with one of the cases gaining consciousness at 6 months.

Indie Itemparative analysis of ipsilateral C1-perfusion data.				
Pre-op mean	Post-op mean	P-value		
CBF-Ipsilateral				
OFC				
57.7	55.49	0.819		
IC				
46.65	63.99	0.034*		
THA				
65.69	83.52	0.170		
CN				
82.44	73.45	0.696		
MSC				
55.96	85.42	0.021*		
Hemispheric mean				
62.37	72.30	0.035*		
MTT-ipsilateral				
OFC				
10.26	8.26	0.382		
IC				
8.43	27.68	0.510		
THA				
8.67	5.81	0.069		
CN				
2.73	8.02	0.517		
MSC				
12.32	8.38	0.037*		

CT: Computed tomography, CBF: Cerebral blood flow, MTT: Mean transit time OFC: Orbitofrontal cortex, IC: Internal capsule, CN: Caudate nucleus, THA: Thalamus, MSC: Motor sensory cortex

On the side of the cranioplasty, the improvement in CBF in IC, MSC, and the total ipsilateral hemispheric mean [Table 1 and Figure 2] were found to be statistically significant. On the contralateral side, an improving trend was seen in the total hemispheric mean CBF, but it did not reach statistical significance [Table 2]. The MTT showed a significant decrease in the MSC region on the ipsilateral side and IC on the contralateral side.

The CSF velocities (mean-V and peak-V), both at the aqueduct of Sylvius [Figure 3] and foramen of Magendie,

Table 2: Comparative analysis of contralateral CT-perfusion data.				
Preoperative mean	Postoperative mean	P-value		
CBF-contralateral				
OFC				
52.66	65.65	0.316		
IC				
55.70	63.37	0.517		
THA				
70.49	82.33	0.304		
CN				
75.04	80.52	0.620		
MSC				
89.70	81.35	0.551		
Hemispheric mean				
68.72	74.65	0.568		
MTT-contralateral				
OFC				
9.22	8.05	0.367		
IC				
28.72	5.93	0.034*		
THA				
7.20	6.16	0.200		
CN				
7.19	5.99	0.096		
MSC				
89.70	6.88	0.144		

CT: Computed tomography, CBF: Cerebral blood flow, MTT: Mean transit time OFC: Orbitofrontal cortex, IC: Internal capsule, CN: Caudate nucleus, THA: Thalamus, MSC: Motor sensory cortex

showed significant improvement in the postoperative period [Table 3]. Reversal of the direction of CSF flow occurring during a cardiac cycle was also noticed in 50% of subjects at aqueduct of Sylvius.

DISCUSSION

The use of DC has resulted in increasing complications such as hydrocephalus, infections, CSF leakage, and syndrome of trephined.^[17,31] The syndrome of trephined or SSFS is a delayed occurrence after a DC which has been hypothesized to be due to derangements in cerebral blood flow, CSF flow abnormalities, and cerebral metabolism.^[13] SSFS shows reversible changes with the early cranioplasty resulting in neurological and functional improvements.^[1,7] As a result, the indication for cranioplasty has shifted from being purely cosmetic to a procedure that aids in early cognitive and functional rehabilitation.^[19]

Although numerous studies have proposed various hypotheses explaining the functional improvement post cranioplasty, no concrete conclusion has been reached. The literature is mainly concentrated on the mechanical effect of the environmental pressure gradient on the unprotected brain parenchyma, along with impaired venous return and changes in CBF.^[26]

Table 3: comparison of CSF velocities at aqueduct of Sylvius and foramen of magendie.

Preoperative mean	Postoperative mean	P-value
Aqueduct of Sylvius		
Mean		
-0.087	0.059	0.000*
Peak		
2.710	3.708	0.000*
Foramen of Magendie		
Mean		
-0.675	0.157	0.001*
Peak		
1.697	2.093	0.007*
CSF: Cerebrospinal fluid		



Figure 2: Left – preoperative perfusion map showing cerebral blood flow (CBF) in motor sensory cortex (MSC) region. Right - postoperative perfusion map showing improvement in CBF in MSC region.

A recent review by Halani et al.[16] concluded that cranioplasty results in an improvement in the ipsilateral CBF, but there is ambiguity regarding the restoration of contralateral CBF. We similarly found a significant improvement in CBF and decreasing MTT on the ipsilateral side, suggestive of improved blood flow with decreased stasis. It is in accordance with the findings of Sarubbo et al.^[27] who also reported a decrease in the MTT values in the early post cranioplasty period. However, the findings of improved CBF in the early post cranioplasty period do not imply a unequivocal long-term increase which is supported by the finding of Wen et al.^[34] reporting ill sustained improvement in CBF over 3 month. Similar results have been reported by Song et al.^[30] in his study on post cranioplasty patients using trans-cranial Doppler. However, Decaminada et al.[6] reported improvement in CBF which was consistently seen till 6 months post cranioplasty. Such discrepancies could arise as a result of differences in the CTP protocol used and the heterogeneity in ROI placement.^[26]

The CSF contained in the craniospinal cavity shows a pulsatile flow in sync with the cardiac cycle, with only a negligible amount of CSF being absorbed during each cycle. As compliance of the craniospinal cavity is the



Figure 3: Left – Peak velocity curve generated from cine magnetic resonance imaging at the aqueduct of Sylvius in the pre-cranioplasty period. Right – improvements in the peak velocity curve seen in the post cranioplasty period.



Figure 4: Graph showing improvement in cognition in two patients who underwent cranioplasty 65 and 84 months after initial trauma, which underlines the role of cranioplasty for improvement in cognition. MoCA: Montreal cognitive assessment score, MMSE: Mini-mental state examination, FAB: Frontal assessment battery.

most important driving factor for this pulsatile CSF flow; therefore, any change in compliance will be reflected in the changing characteristics of the CSF flow.^[22] Indeed, the changes in CSF dynamics have been well documented in the literature, with studies reporting a significant reduction in the CSF pulse wave amplitude in post-craniectomy patients, which has shown improvement after cranioplasty.^[20,21] Fodstad et al.,^[12] reporting on a series of 40 post-cranioplasty patients demonstrated improved CSF hydrodynamics using a CSF infusion test, which correlated with symptomatic improvement. Dujovny et al.[10] showed improved CSF flow and peak CSF velocity using the cine MRI technique in a single cranioplasty case. Using PC MRI to assess the change in CSF velocities, we found improvement in the mean as well as peak CSF velocities, measured both at the aqueduct of Sylvius and the foramen of Magendie. The change in the CSF flow characteristics has been proposed to be due to a decrease in the compliance of the cranial cavity as well as increased arterial pulsatility seen after repositioning of the bone flap, making the cranium a closed cavity.^[3,29]

Our study shows significant improvement in cognitive outcomes observed over 24 weeks after cranioplasty. The mean MoCA, MMSE, and FAB scores showed significant improvement in the mean scores compared to the baseline scores at 6 months. The mean time elapsed between craniectomy and cranioplasty was 16.46 months. As most of the neurological recovery after traumatic brain injury happens within the 1st year, therefore, the neurocognitive improvement is more likely an effect of cranioplasty. We had two outlier patients who underwent cranioplasty at 65 and 84 months after initial surgery and still showed significant improvement in the test scores [Figure 4] (baseline score: MMSE-20, 4; MoCA-15, 3; FAB-9, 3 and scores at 6 months: MMSE-24, 10; MoCA-21, 11; FAB-11, 9). Another patient who had cranioplasty at 44 months also experienced a 5- and 6-point improvement in MoCA and FAB scores, respectively. These cases are noteworthy as these patients showed remarkable improvement in neurocognitive abilities at just 6 months post-surgery, especially considering it had already been more than 5 years since the initial event for the first two cases. Our experience with these cases emphasizes the role of cranioplasty in the observed cognitive improvement. The overall trend suggested a significant improvement in neurocognitive outcome, which is most likely due to the improvement in blood flow (improved CBF and decreased MTT), improved intracranial CSF dynamics, along increased cerebral metabolism and glymphatic flow.^[25,35] Our results further emphasize that the improvement in blood flow is a regional phenomenon with predominantly ipsilateral improvement. However, the changes in CSF dynamics (mean and peak velocity) were consistently observed at both the aqueduct of Sylvius and the foramen of Magendie, which attained very high statistical significance with more than 50% of patients attaining reversal of flow. Therefore, the change in the CSF dynamics is a more consistent phenomenon that may play a more significant role in shaping neurocognitive outcomes.

Although we are reporting, to the best of our knowledge, the largest series of cranioplasty patients being evaluated by both CTP and Cine MRI studies along with neurocognition, a few limitations are obvious. The study population consists of head injury patients undergoing craniectomy due to a variety of pathologies ranging from subdural hematoma to parenchymal brain contusions. Moreover, the size of the craniectomy defect varied among individual patients. The CTP and Cine MRI studies were done at a single point of time (7 days before and after surgery), which could provide a potential source of bias due to inherent errors associated with point observations. The study population size limits the statistical power of the results.

CONCLUSION

Cranioplasty leads to marked and consistent improvement in CSF circulation and flow along with improved cerebral hemodynamics, specially on the ipsilateral side. Improved cerebral perfusion and, more importantly, CSF dynamics may be responsible for the demonstrable improvement in the neurocognition in the post-cranioplasty period.

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Ethical approval

The Institutional Review Board approved the research/study at the Office of the Ethics Committee, SMS Medical College and attached hospitals, Jaipur, number 161 MC/EC/2018, dated May 15, 2020.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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