Circulating Brain-Injury Markers After Surgery for Craniosynostosis

Isak Michaëlsson[1,2], Thomas Skoglund[1,2], Tobias Hallén[1,2], Robert Olsson[2], Giovanni Maltese[3], Peter Tarnow[3], Madiha Bhatti-Søfteland[3], Henrik Zetterberg[4-8], Kaj Blennow[4], Lars Kölby[3]

OBJECTIVE: **Historically, there have been few quantitative methods for effectively evaluating outcomes after surgery for craniosynostosis. In this prospective study, we assessed a novel approach for detecting possible post-surgery brain injury in patients with craniosynostosis.**

METHODS: **We included consecutive patients operated on for sagittal (pi-plasty or craniotomy combined with springs) or metopic (frontal remodeling) synostosis at the Craniofacial Unit at Sahlgrenska University Hospital, Gothenburg, Sweden, from January 2019 to September 2020. Plasma concentrations of the brain-injury biomarkers neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and tau were measured immediately before induction of anesthesia, immediately before and after surgery, and on the first and the third postoperative days using single-molecule array assays.**

RESULTS: **Of the 74 patients included, 44 underwent craniotomy combined with springs for sagittal synostosis, 10 underwent pi-plasty for sagittal synostosis, and 20 underwent frontal remodeling for metopic synostosis. Compared with baseline, GFAP level showed a maximal significant increase at day 1 after frontal remodeling for metopic synostosis and pi-plasty ($P = 0.0004$ and $P = 0.003$, respectively). By contrast, craniotomy combined with springs for sagittal synostosis showed no increase in GFAP. For neurofilament light, we found a maximal significant increase at day 3 after surgery for all procedures, with significantly higher levels observed after frontal remodeling and pi-plasty compared with craniotomy combined with springs ($P < 0.001$).**

CONCLUSIONS: **These represent the first results showing significantly increased plasma levels of brain-injury biomarkers after surgery for craniosynostosis. Furthermore, we found that more extensive cranial vault procedures resulted in higher levels of these biomarkers relative to less extensive procedures.**

INTRODUCTION

The indications for surgery for craniosynostosis include achievement of shape correction, reducing the risk of increased intracranial pressure, and promoting beneficial neurocognitive development. The introduction of new surgical techniques often shows that less invasive techniques are capable of producing results comparable to those associated with more invasive procedures.[1] Several factors influence the final outcome, and the tentative benefits for one outcome may impose negative effects on another (e.g., shape correction vs. intracranial volume [ICV]). Previous studies report instances of normal ICV before surgery but subsequent reductions at later follow-up related to both sagittal synostosis and metopic synostosis.[2,3] The underlying

Key words
- Brain-injury markers
- Cranioplasty
- Craniotomy
- Pi-plasty
- Springs

Abbreviations and Acronyms
ELISA: Enzyme-linked immunosorbent assay
GFAP: Glial fibrillary acidic protein
ICV: Intracranial volume
IQR: Interquartile range
NfL: Neurofilament light

From the [1]Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg; [2]Department of Neurosurgery, Sahlgrenska University Hospital; [3]Department of Plastic Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, University of Gothenburg; [4]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden; [5]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom; [6]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; [7]UK Dementia Research Institute at UCL, London, United Kingdom; and [8]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

To whom correspondence should be addressed: Lars Kölby, M.D., Ph.D. [E-mail: lars.kolby@surgery.gu.se]

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mechanism for the reduction in ICV may be the osseous trauma imposed by surgery, which is supported by results showing that a less invasive procedure results in better ICV-related outcomes than a more extensive procedure.[3]

Studies suggest that the duration of anesthesia is important to surgical outcomes, because longer anesthesia is reportedly harmful to cognitive development; however, other factors can also affect outcomes, making any effect of anesthesia difficult to isolate.[4] One example is the conflicting roles of anesthesia during surgery related to blood pressure and blood loss, in which hypotensive anesthesia can reduce blood loss and also possibly impair cerebral oxygenation.[5] Similarly, the beneficial effects of cranioplasty on neurocognitive development are difficult to prove. In general, children with isolated synostosis show normal cognitive functions[6]; however, there are few unbiased comparisons in the literature.

In addition, the negative effects on cerebral tissue at the cellular level in response to surgery for craniosynostosis cannot be measured. However, the development of ultrasensitive assays[7,8] for circulating brain-injury biomarkers has enabled assessment of the neuronal effects of skull surgery. Such markers have proved useful for evaluating brain damage after head trauma[9] and after intracranial surgical procedures,[10] as well as among neonates undergoing cardiac surgery.[11]

Given the difficulty in quantifying the effects of surgery for craniosynostosis on improving specific outcomes, these new circulating biomarkers may contribute to a further understanding of the impact of craniosynostosis surgery on the brain. In this study, we prospectively evaluated levels of circulating biomarkers of brain injury in response to cranioplasty for craniosynostosis to evaluate their potential as markers for determining surgical response.

METHODS

Patients and Procedures

We included all consecutive patients operated on for sagittal synostosis or metopic synostosis at the Craniofacial Unit at Sahlgrenska University Hospital, Gothenburg, Sweden, from January 2019 to September 2020. The study was approved by the Gothenburg Ethics Committee (approval number 300:18).

Sagittal synostosis was operated on either by craniotomy combined with springs if the child was younger than 6 months or pi-plasty if the child was >6 months old at the time of surgery. Metopic synostosis was operated on with frontal remodeling combined with a spring or bone transplant in the glabellar region if the child was operated on before or after 6 months of age, respectively.

For procedures involving springs, these patients underwent spring extraction 6 months after insertion.

Blood Sampling

For the primary operation, blood samples were collected immediately before induction of anesthesia (if possible), immediately before the start of surgery, at surgery completion, and on the first and the third postoperative days. A total of 2 mL of blood was collected at each time point.

Biomarker Analysis

Blood samples were placed in Vacutainer tubes (BD Biosciences, Franklin Lakes, New Jersey, USA) and centrifuged for 10 minutes at 3800 rpm, followed by transfer of plasma in 0.2-mL aliquots to cryotubes. The samples were stored at −70°C before being transported to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Sweden, for analysis.

Concentrations of total tau and glial fibrillary acidic protein (GFAP) in plasma were measured with a single-molecule array (Simoa) HD-1 analyzer (Quanterix, Billerica, Massachusetts, USA) using commercially available digital enzyme-linked immunosorbent assay (ELISA) reagents. The concentration of neurofilament light (NfL) in plasma was measured on the Simoa platform using in-house digital ELISA reagents, as previously described.[12] All measurements were performed by board-certified laboratory technicians blind to the clinical information. All samples were analyzed in 1 single round of experiments, with intra-assay coefficients of variation of <10% for all biomarkers.

Statistical Analysis

Patient characteristics are presented as the mean ± standard deviation or numbers with percentages. Nonparametric tests were used for statistical analyses of preoperative and postoperative levels of the biomarkers because of a skewed data distribution. Absolute concentration changes from baseline were used to visualize temporal profiles and for all calculations.[13] The Wilcoxon signed-rank test was used for paired analyses, and a Kruskal-Wallis test or Mann-Whitney U test was used for comparisons between groups depending on the number of groups. Correlations between continuous data values were assessed using the Spearman correlation coefficient. All tests were 2-sided, and $P < 0.05$ was considered significant.

RESULTS

Patient Characteristics

Seventy-four patients (58 men and 16 women; mean age, 180 ± 61 days) were included in the study. Forty-four patients underwent craniotomy combined with springs for sagittal synostosis, 10 underwent pi-plasty for sagittal synostosis, and 20 underwent frontal remodeling for metopic synostosis. The duration of surgery was significantly longer for patients undergoing pi-plasty and frontal remodeling compared with those undergoing craniotomy combined with springs ($P < 0.001$). In addition, the amount of bleeding and need for transfusion were significantly greater for the patients undergoing pi-plasty and frontal remodeling compared with levels observed for patients undergoing craniotomy combined with springs ($P < 0.001$). Patient characteristics are presented in Table 1.

Evaluation of Postsurgery Changes in Plasma Biomarkers

GFAP Level After Craniotomy Combined with Springs for Sagittal Synostosis. We found significant reductions in GFAP level at all postoperative time points, with a nadir observed immediately after surgery ($P < 0.001$). The median concentrations were 136.0 pg/mL (interquartile range [IQR], 103.0–174.0 pg/mL), 256.0 pg/mL (IQR, 185.0–354.0 pg/mL), and 255.0 pg/mL (IQR, 179.0–326.0

Table 1. Baseline Demographic and Clinical Characteristics of Patients ($N = 74$)

Characteristics	Values
Gender, n (%)	
Male	58 (78)
Female	16 (22)
Type of surgery, n (%)	
Craniotomy combined with springs for sagittal synostosis	44 (59)
Pi-plasty for sagittal synostosis	10 (14)
Frontal remodeling for metopic synostosis	20 (27)
Duration of surgery (minutes), mean (SD)	
Craniotomy combined with springs	64.8 (19.6)
Pi-plasty	122.2 (10.3)
Frontal remodeling	156.6 (16.6)
Age (days), mean (SD)	
Craniotomy combined with springs	151.0 (24.6)
Pi-plasty	284.2 (44.2)
Frontal remodeling	190.5 (64.8)
Bleeding (mL), mean (SD)	
Craniotomy combined with springs	38.4 (33.7)
Pi-plasty	188.0 (89.9)
Frontal remodeling	213.3 (92.5)
Perioperative blood transfusion (mL), mean (SD)	
Craniotomy combined with springs	28.5 (43.9)
Pi-plasty	207.4 (66.4)
Frontal remodeling	210.9 (77.5)

SD, standard deviation.

pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

GFAP Level After Pi-Plasty for Sagittal Synostosis. We found a significant reduction in GFAP level immediately after surgery ($P = 0.005$), followed by a significant increase at day 1 after surgery ($P = 0.005$). The median concentrations were 126.0 pg/mL (IQR, 72.8–183.8 pg/mL), 727.5 pg/mL (IQR, 388.8–832.0 pg/mL), and 349.0 pg/mL (IQR, 175.5–412.3 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

GFAP Level After Frontal Remodeling for Metopic Synostosis. GFAP level showed an initial reduction immediately after surgery, followed by a significant increase at day 1 after surgery ($P < 0.001$). The median concentrations were 196.0 pg/mL (IQR, 101.3–315.8 pg/mL), 535.0 pg/mL (IQR, 295.3–750.8 pg/mL), and 220.0 pg/mL (IQR, 155.5–307.0 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively. We subsequently used peak GFAP levels at day 1 after surgery for further analyses for all patients.

NfL Level After Craniotomy Combined with Springs for Sagittal Synostosis. We found a significant reduction in NfL level immediately after surgery and at day 1 after surgery, followed by a significant increase at day 3 after surgery. The median concentrations were 5.89 pg/mL (IQR, 4.83–8.32 pg/mL), 10.45 pg/mL (IQR, 8.91–14.4 pg/mL), and 18.1 pg/mL (IQR, 15.7–25.0 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

NfL Level After Pi-Plasty for Sagittal Synostosis. NfL showed an initial significant reduction immediately after surgery ($P = 0.003$), followed by an increase at day 1 after surgery ($P = 0.059$) and an even larger increase at day 3 after surgery ($P = 0.012$). The median concentrations were 3.72 pg/mL (IQR, 2.84–5.35 pg/mL), 9.7 pg/mL (IQR, 14.5–23.15 pg/mL), and 53.35 pg/mL (IQR, 37.8–68.28 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

NfL Level After Frontal Remodeling for Metopic Synostosis. NfL level showed an initial significant reduction immediately after surgery ($P = 0.006$), followed by a significant increase at day 1 after surgery ($P < 0.001$) and an even larger increase at day 3 after surgery ($P \leq 0.001$). The median concentrations were 6.19 pg/mL (IQR, 4.17–9.02 pg/mL), 18.6 pg/mL (IQR, 13.15–24.15 pg/mL), and 65.3 pg/mL (IQR, 46.15–83.8 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively. We subsequently used peak NfL level at day 3 after surgery for further analyses for all patients.

Tau Level After Craniotomy Combined with Springs for Sagittal Synostosis. Tau level showed a significant reduction at all postoperative time points, with a nadir observed at day 3 after surgery ($P < 0.001$). The median concentrations were 3.84 pg/mL (IQR, 3.13–5.11 pg/mL), 3.61 pg/mL (IQR, 2.48–4.79 pg/mL), and 3.31 pg/mL (IQR, 2.45–4.13 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

Tau Level After Pi-Plasty for Sagittal Synostosis. Tau level showed a significant reduction at day 3 after surgery ($P = 0.017$). The median concentrations were 3.65 pg/mL (IQR, 2.3–4.66 pg/mL), 4.05 pg/mL (IQR, 2.64–4.66), and 1.85 pg/mL (IQR, 1.58–3.32 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

Tau Level After Frontal Remodeling for Metopic Synostosis. Tau level showed no significant changes at any time point. The median concentrations were 3.65 pg/mL (IQR, 3.0–5.26 pg/mL), 4.17 pg/mL (IQR, 3.34–5.52 pg/mL), and 2.97 pg/mL (IQR, 2.73–4.1 pg/mL) immediately after surgery and at days 1 and 3 after surgery, respectively.

Comparisons Between Surgical Techniques. Both pi-plasty for sagittal synostosis and frontal remodeling for metopic synostosis showed significantly greater increases in NfL at days 1 ($P < 0.001$ for both) and 3 ($P < 0.001$ for both) after surgery and in GFAP at day 1 after surgery ($P < 0.001$ for both) compared with craniotomy combined with springs for sagittal synostosis. We observed no significant differences associated with increases in tau level between the different groups. Figures 1–3 show visual representations of the changes in biomarker levels according to surgical technique.

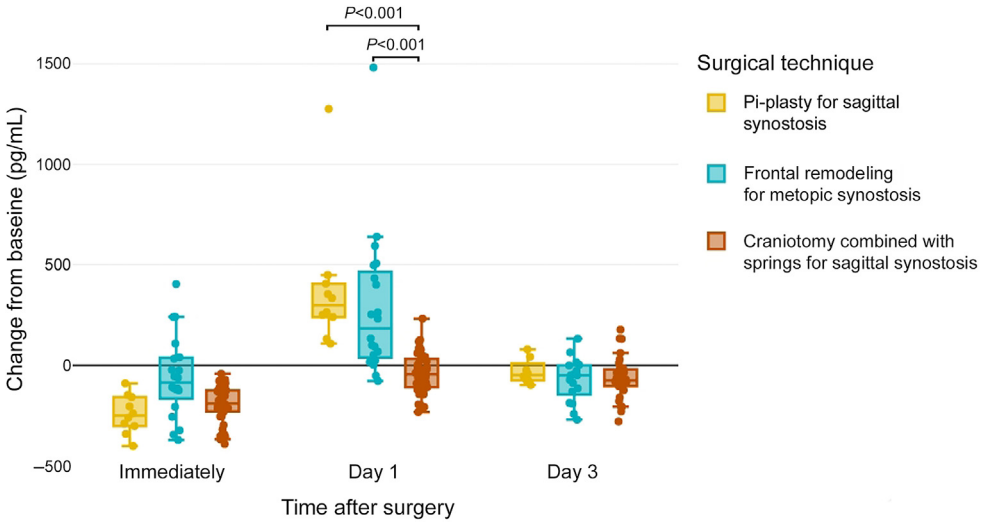

Figure 1. Visual representation of differences in the relative change from baseline glial fibrillary acidic protein level after surgery. At day 1 after surgery, increases in glial fibrillary acidic protein level were larger for both the extensive cranioplasties relative to those related to the less extensive craniotomy combined with springs.

Influence of Background Variables on Biomarker Levels. Age ($P < 0.001$), length of surgery ($P < 0.001$), bleeding ($P < 0.001$), amount of blood transfusion ($P < 0.001$), and amount of fluids given perioperatively ($P < 0.001$) all correlated with increases in GFAP level at day 1 and NfL level at day 3 after surgery.

DISCUSSION

This represents the first study showing that cranioplasty for craniosynostosis elicits increased levels of markers for brain injury.

Circulating markers of brain injury are increased in proportion to the cerebral damage inflicted by brain surgery, severe trauma, neurodegenerative disease, and brain tumors, with these changes detectable in both cerebrospinal fluid and peripheral blood.[14-16] The ability to measure circulating markers of neuronal damage has emerged in response to developments in analytical methods targeting neurofilaments, with ultrasensitive immunoassays, such as Simoa, allowing the detection of biomarkers at the pg/mL range and reliable quantification in peripheral blood. As a result, markers of brain injury have recently gained increasing interest according to their detection in various clinical contexts of brain injury, including after concussions. Specifically, GFAP was identified as a marker for traumatic brain injury in patients with normal computed tomography scans after head trauma,[17] and circulating markers of brain injury have been used to predict long-term outcomes after mild brain injury.[18]

Surgery for isolated craniosynostosis ranges from very extensive procedures (e.g., total vault remodeling) to less extensive procedures (e.g., craniotomy combined with springs in sagittal synostosis). Important indications for the operation include prevention of increased intracranial pressure, allowance of beneficial neurocognitive development, and the correction of head shape. Outcome measures traditionally include the degree of shape correction, calculation of complication rates, and descriptions of the incidence of increased intracranial pressure.[19] In metopic synostosis, the incidence of increased intracranial pressure is low,[20] because surgery does not alter cortical circulation[21]; therefore, shape correction remains the most important indication for surgery in metopic synostosis.

A more functional surgical outcome would be neuropsychological development. A previous study identified an increased prevalence of neurodevelopmental issues in isolated synostosis[22]; however, definitive proof of the beneficial effect of surgery in that respect remains lacking. In addition, a study of neurocognitive outcomes in children who had undergone neonatal cardiac surgery reported a negative association between high GFAP and neurocognitive outcome at 1 year of age.[11] These findings support advocating for less extensive surgery for craniosynostosis. In the present study, we clearly identified differences in increased levels of the targeted biomarkers after the more extensive procedures, whereas less extensive procedures (e.g., craniotomy combined with springs) elicited minimal effects on marker levels.

GFAP is a protein specifically expressed in astrocytes,[23] whereas NfL is expressed in both central and peripheral neurons.[24] The increased NfL levels detected in the present study were arguably present in central neurons, given that minimal changes in these levels were observed after craniotomy combined with springs,

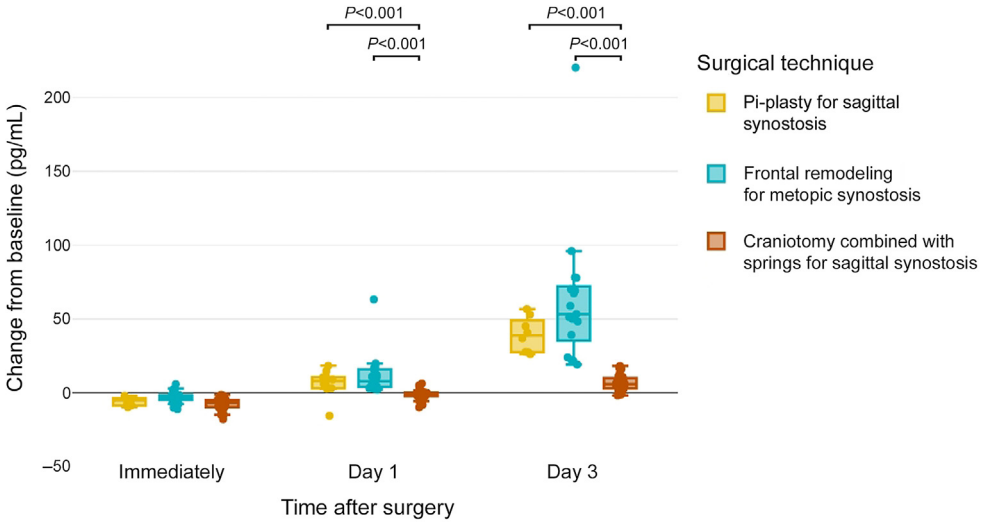

Figure 2. Visual representation of differences in the relative change from baseline neurofilament light level after surgery. At day 3 after surgery, increases in neurofilament light level were larger for both the extensive cranioplasties relative to those related to less extensive craniotomy combined with springs.

despite the need for a skin incision approximately 50% the length of the bicoronal incision required in more extensive operations.

The clinical importance of the present findings remains unclear. The data points collected were limited to those obtained before and after surgery and across a 3-day period in very young patients. However, evidence supporting NfL as a marker capable of reporting the severity of brain damage after concussion[9] and predictive of cognitive impairment in various diseases[25-28] suggests that its increase after surgery for craniosynostosis might reflect a neuronal effect that could have clinical importance for

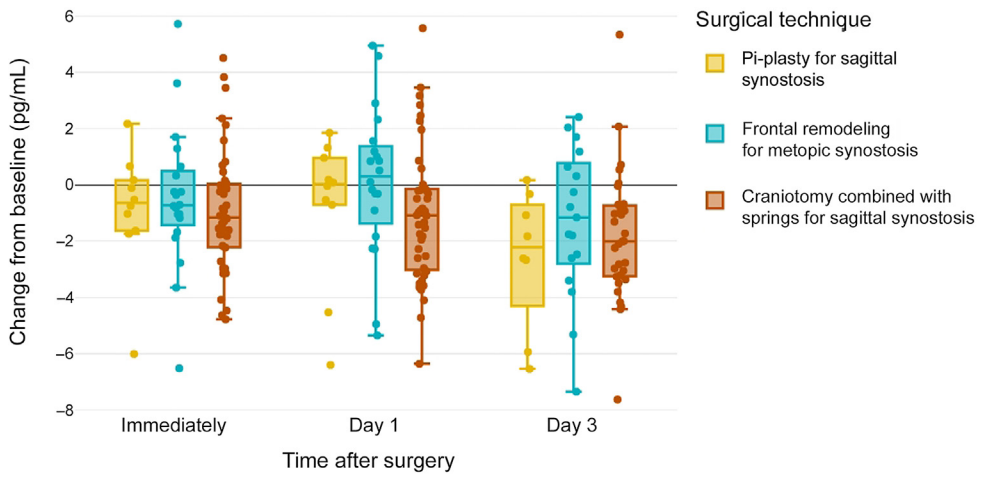

Figure 3. Visual representation of differences in the relative change from baseline tau level after surgery between the different surgical techniques. Tau levels remained stable during the 3-day study period irrespective of surgical method.

long-term brain function. It is possible that the current difficulties in showing the beneficial effects of surgical correction on neurocognitive development could be partly explained by negative surgery-related effects on the brain, which might be reflected by increased levels of the biomarkers targeted in the present study.

The results identified correlations of age, length of surgery, perioperative bleeding, amount of blood transfusion, and amount of fluids administered perioperatively with increases in both GFAP and NfL levels. After an initial slight decline, likely caused by hemodilution from intravenous fluids, we specifically observed these increased levels in patients undergoing the more extensive rather than less extensive procedures. Although the precise mechanisms underlying these correlations remain to be identified, a possible explanation might involve temporarily reduced cerebral oxygenation.[29]

This study has several limitations. The increased levels of brain-injury markers identified in this study were moderate relative to those reported after intracerebral surgery and, in general terms, it is reasonable to argue that a more pronounced increase in these levels would likely signify worse outcomes. However, ELISA does not allow comparisons of absolute values between different sets of analyses; therefore, we analyzed all samples at the same time to allow for comparisons. In addition, it is difficult to make relevant comparisons of the marker levels measured in the present study with those of previous studies based on the differences in methodology and patient cohorts. Further studies to identify normal levels of these biomarkers in infants, as well as levels after various procedures and in association with conditions that affect the central nervous system, would be valuable. Moreover, possible confounders, such as age and body weight, need to be addressed when trying to establish reference values. Furthermore, assessments of marker levels were continued only up to 3 days after surgery. An extended sampling period to clarify how long these increased levels are maintained would be informative. In this case, increased levels of these markers for an extended period after surgery would likely support the clinical importance of the neurotrauma inflicted by the operation. Another limitation of the study is that craniotomy combined with springs includes a second operation for spring extraction and that sampling in connection with the latter procedure was unfeasible because of the absence of a central venous catheter during this procedure.

CONCLUSIONS

This is the first study showing objective measurements of potential brain damage inflicted by surgery for craniosynostosis. The findings identified greater changes in levels of brain-injury biomarkers after more extensive surgical procedures. Furthermore, these findings support the potential use of these biomarkers for determining postsurgical outcomes related to cranioplasty procedures.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Isak Michaëlsson: Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Thomas Skoglund:** Study planning, Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Tobias Hallén:** Study planning, Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Robert Olsson:** Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Giovanni Maltese:** Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Peter Tarnow:** Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Madiha Bhatti-Søfteland:** Investigation, Formal analysis, Writing — original draft, Approval of final draft. **Henrik Zetterberg:** Conceptualization, Methodology, Formal analysis, Writing — original draft, Approval of final draft. **Kaj Blennow:** Conceptualization, Methodology, Formal analysis, Writing — original draft, Approval of final draft. **Lars Kölby:** Conceptualization, Investigation, Formal analysis, Writing — original draft, Approval of final draft.

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