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Research Article

Brain Injury Biomarkers in Humans Undergoing General Anaesthesia and Noncerebral Surgery

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Introduction: This study is aimed at investigating brain injury biomarkers neurofilament light (NfL), tau, neuron-specific enolase (NSE), calcium-binding protein S100B (S100B) and glial fibrillary acidic protein (GFAP) in blood during general anaesthesia and abdominal surgery in patients without cerebral injury, to evaluate the effect of general anaesthesia and surgery per se on the release of these biomarkers.
Methods: This prospective observational study was conducted at Sahlgrenska University Hospital, Gothenburg, Sweden, between September and November 2021. Patients scheduled for mixed abdominal surgery under general anaesthesia were included. Vital parameters and near-infrared spectroscopy (NIRS) for cerebral perfusion were continuously monitored. Blood pressure was kept close to each patients' preanaesthetic mean arterial pressure. Vasopressors and fluids were administered at the discretion of the attending physician, not influenced by the study.
Results: There were 23 patients (11 females [48%] and 12 males [52%]) included in the study. NfL, tau, NSE and S100B increased significantly when 2- and 24-h concentrations were compared with preoperative values, whilst GFAP did not. The continuous mean arterial blood pressure was 83.5 mmHg, with a 62.2–90.4 mmHg range. The mean NIRS was 77.5% (range 62.2–90.4). No patient had a drop in NIRS of 12% or more. Postoperative symptoms of confusion or neurological deficits were not observed in any patient within 48 h from the start of anaesthesia.

Conclusion: General anaesthesia and abdominal surgery in patients with well-maintained cerebral perfusion and no clinical signs of postoperative cerebral injury caused an increase in levels of brain injury biomarkers NfL, tau, NSE and S100B in blood. Interestingly, there was no increase in levels of GFAP in the blood. These data suggest that GFAP is the only biomarker, amongst the investigated biomarkers, which is not released into the bloodstream during general anaesthesia and surgery in patients with no suspected brain injury. More extensive studies on this subject are warranted.

Trial Registration: ClinicalTrials.gov identifier: NCT03919370.

1. Introduction

Prompt detection and treatment of cerebral hypoperfusion is of essence to avoid manifest cerebral injury. In cardiology, cardiac ischemia has been detectable with a simple blood sample, analysing cardiac biomarkers troponin T and I for decades [1]. A corresponding biomarker for cerebral ischemia would be of great value, especially for anaesthetised or sedated patients where cerebral ischemia is challenging to detect since the patient cannot be neurologically examined. A brain injury biomarker could potentially be used to confirm or dismiss cerebral injury in patients that are sedated in intensive care, undergoing surgery or who are unconscious. The optimal brain injury biomarker should be highly brain-specific, have a high temporal resolution and be unaffected by any extracranial trauma, as well as by noncerebral surgery and anaesthesia per se.

There are several potential candidates, such as neurofilament light (NfL), tau, neuron-specific enolase (NSE), calcium-binding protein S100 beta (S100B) and glial fibrillary acidic protein (GFAP) [2]. However, the added aspect of simultaneous procedures, such as anaesthesia and surgery, makes the interpretation of these biomarkers more challenging, since several of them also exist in other organs and tissues apart from the central nervous system.

NfL is primarily present in myelinated axons but also in other parts of the neuron and is not specific to the central nervous system [3, 4]. It is mainly regarded as a general marker of neuroaxonal injury, irrespective of underlying cause [5]. It is currently used for predicting hypoxic encephalopathy after cardiac arrest and to predict outcomes after ischemic stroke [6, 7]. Tau is primarily present in unmyelinated axons in the peripheral and central nervous systems [8] and is suggested for use in clinical praxis to prognosticate outcomes after cardiac arrest [9]. However, it is also prevalent in the kidney and liver, which attenuates its usability as a brain injury biomarker during abdominal surgery [10]. Since tau and NfL are also present in the peripheral nervous system, they could be released or leaked into the bloodstream during noncerebral surgery [11]. In turn, NSE, widely used for predicting outcomes after cardiac arrest [12], is primarily present in the neuronal cell bodies but also in high concentrations in red blood cells and platelets [13], which could make it an unsuitable biomarker for patients undergoing surgery due to hemolysis [13]. S100B is a well-known biomarker for traumatic brain injury, but it is also prevalent in skeletal muscle and adipose tissue. It may thus be released into the bloodstream during surgery. It could possibly also be released from traumatic injuries, but research on this topic is scarce [14, 15]. GFAP is consistently reported as the most brain-specific of these biomarkers and has been investigated as a biomarker in traumatic and hypoxic brain injury but also in haemorrhagic stroke [16–18].

This study is aimed at investigating to what extent the brain injury biomarkers NfL, tau, NSE, S100B and GFAP are released into the bloodstream during general anaesthesia and noncerebral surgery in patients with well-maintained cerebral perfusion and no evident postoperative clinical signs of cerebral injury.

2. Methods

2.1. Setting. The data collection for this prospective observational study was conducted at the Sahlgrenska University Hospital, Gothenburg, Sweden, between September and November 2021 and is part of the larger project Cerebral Ischemia Detection using Artificial Intelligence (CIDAI) aimed at finding ways to detect cerebral ischemia in unconscious or sedated patients. The study protocol for CIDAI was published in 2020 [19] and has since been supplemented with biomarkers in blood. This study was approved by the Swedish Ethical Review Authority (Dnr 2020-00169) on 2020-03-10, with amendment 2020-05122 on 2020-10-31, and the study protocol adheres to the latest version of the Declaration of Helsinki. This manuscript adheres to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

2.2. Patients and Procedures. Patients scheduled to undergo mixed abdominal surgery under general anaesthesia between September and November 2021 were eligible for inclusion in this study. As the study set-up required the constant presence of a research assistant or PhD student, not all patients on the operating schedule during the study period were screened for inclusion. Instead, eligible patients were identified when the resources were available for research. Exclusion criteria were: history of ischaemic stroke or traumatic brain injury, pre-existing neurological disease, and atrial fibrillation, as these may cause disturbances in the data collection for the main study CIDAI, which includes recording of heart rate variability and electroencephalography. Written informed consent was obtained from all patients. The patients were scheduled to undergo surgery either in the Trendelenburg or supine position as per the hospital protocols, depending on the procedure. Body position was not influenced by study participation.

2.3. Data Collection. Anaesthesia procedures and decisions were not influenced by the study and were left to the discretion of the attending physician. No anaesthesia depth

monitoring device was applied to the patients in this study. Physiological parameters, such as heart rate, blood pressure and lacrimation, were used as surrogate markers. All patients had standard monitoring of vital parameters, including oxygen saturation, electrocardiography, continuous blood pressure, body temperature and end-tidal carbon dioxide level monitoring. The monitor and anaesthesia delivery system used was Maquet Flow-i-C20. Anaesthesia was induced with propofol and fentanyl or propofol and remifentanil. Maintenance was obtained with sevoflurane combined with fentanyl boluses, or with a continuous remifentanil infusion. All patients received the muscle relaxant rocuronium, underwent endotracheal intubation and were mechanically ventilated.

2.4. Study-Specific Measures—Blood Pressure Control, NIRS and Follow-Up. The only study-specific monitoring device was near-infrared spectroscopy (NIRS). Electrodes for measurement were attached to the forehead before the start of anaesthesia to monitor changes in regional oxygen saturation (rSO_2) of blood in the frontal cerebral circulation (INVOS). NIRS is commonly used as a surrogate measure of cerebral perfusion [21]. However, NIRS can only determine oxygenation in tissues close to the attachment site and may not accurately measure cerebral oxygenation in all areas of the brain [22]. A drop in NIRS of 12% or more compared to preanaesthesia levels is considered a reliable threshold for intraoperative cerebral hypoperfusion, as suggested by Wang et al. [23]. An arterial line was placed preanaesthesia, providing continuous invasive blood pressure monitoring. If an arterial line could not be established, the blood pressure monitoring was performed noninvasively every 5 min. Throughout the procedure, blood pressure was kept as close as possible to each patients' preanaesthetic mean arterial pressure (MAP). Vasopressors were administered at the discretion of the attending physician: norepinephrine in infusion, phenylephrine or ephedrine in boluses.

2.5. Follow-Up. All patients were followed for 48 h after termination of surgery or until discharged. Patients remained at the postoperative intensive care unit for a minimum of 6 h. They were assessed by an anaesthetist and a specialist nurse regarding physiological parameters, confusion, neurological deficits, pain, nausea, and surgical complications before discharge to an ordinary ward as per hospital protocols. Following admission to the ward, assessments were made by the attending nurse, physiotherapist and attending surgeons. Physiological parameters, confusion, pain and surgical complications were registered using the National Early Warning Score Chart (NEWS 2) [24, 25].

2.6. Sample Collection and Biomarker Analysis. Blood samples were obtained preoperatively, as well as 2 and 24 h postoperatively, to create a timeline for the biomarker release trajectory. One sample was obtained at baseline, and one sample was conducted to assess the response to anaesthesia and surgery and a further sample to determine whether the levels of biomarkers continued to rise or began to decrease postoperatively. The blood samples were collected in serum and plasma tubes, respectively, centrifuged, aliquoted, and stored at −80°C. All samples were analysed at the Clinical Neurochemistry Laboratory of the Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Mölndal Campus, Sweden.

The plasma concentration of NfL, tau and GFAP were measured using the Simoa (Single molecule array) Neurology 4-plex assay kit (Quanterix, Billerica, Massachusetts) on an HD-X Analyser. Simoa is an automated immunoassay platform with femtoliter reaction chambers that utilises antianalyte antibodies conjugated to magnetic beads with biotinylated antibodies to create a digitally detectable fluorescent immunocomplex. Serum concentrations of NSE and S100B were measured using an electrochemiluminescence immunoassay kit on a Cobas e601 (Roche Diagnostics, Rotkreuz, Switzerland). All samples were analysed concurrently using one batch of reagents by board-certified laboratory technicians blinded to the clinical data. Intra-assay coefficients of variation were < 10%.

2.7. Statistical Analyses. Data were tested for normal distribution using the Shapiro–Wilk test. Data are presented as the median with interquartile range (IQR) or full range (min–max) when appropriate, or as mean with standard deviation (SD). Descriptive statistics were used to describe patient characteristics. Related samples Friedman's two-way analysis of variance by ranks was used to compare the baseline values preoperatively to the samples from 2 and 24 h, postoperatively. Extreme outliers (> 3 SDs) occurred in the original dataset for all biomarkers except for GFAP. These were removed from the original dataset before calculations were made. No further exclusions were made after that. Data were analysed using SPSS 28.0.1.1 software package (IBM Corp., Armonk, New York, United States).

3. Results

There were 23 patients (11 females [48%] and 12 males [52%]) included in the study. Table 1 presents the patient characteristics.

3.1. Anaesthesia Procedures. The induction dose of propofol was 2–4 mg/kg bodyweight, and remifentanil was administered via an infusion pump preprogrammed for target-controlled infusion (TCI). Parameters including patient weight, gender, and age were entered when programming the pump. For patients receiving fentanyl at induction, a dose of 150–200 μg was used. Rocuronium, at 0.6 mg/kg, was administered to all patients as a muscle relaxant. Anaesthesia maintenance was achieved with the volatile agent sevoflurane. The minimum alveolar concentration (MAC) ranged from 0.54 to 1.24. The fentanyl dosage postinduction ranged from 50 to 150 μg. Hypotension was managed with bolus doses of ephedrine, with a total administered amount ranging from 5 to 45 mg per patient. One patient received a norepinephrine infusion of 0.05–0.1 μg/kg/min, and three patients received phenylephrine bolus doses of 0.1–0.3 mg. Crystalloid fluids were infused, with all patients receiving 1–2 L of crystalloid fluids during the surgery. All patients

TABLE 1: Patient characteristics.

	(*n* = 23)
Age	
Mean years (SD)	66 (11.1)
Sex	
Female, *n* (%)	11 (47.8)
BMI mean (SD)	26.2 (5.3)
ASA score	
1	5
2	16
3	2
4	0
Comorbidities	
Hypertension, *n* (%)	10 (43.5)
Diabetes, *n* (%)	3 (13.0)
Smoking, *n* (%)	1 (4.3)
Chronic kidney disease, *n* (%)	1 (4.3)
Congestive heart failure, *n* (%)	0
Type of surgery	
Robot-assisted laparoscopic prostatectomy *n* (%)	9 (39)
Robot-assisted laparoscopic hysterectomy *n* (%)	8 (34.7)
Hysterectomy open *n* (%)	1 (4.3)
Robot-assisted kidney resection *n* (%)	2 (8.7)
Hemicolectomy laparoscopic *n* (%)	1 (4.3)
Hemicolectomy open *n* (%)	1 (4.3)
Kidney pyeloplasty *n* (%)	1 (4.3)
Trendelenburg position *n* (%)	17 (74)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

had a positive perioperative fluid balance of 0.4–1.8 L. The surgical procedures for this study are described in Table 1. The mean (SD) duration of surgery was $156 \pm (68)$ min.

3.2. Sampling. Three blood samples were missing, one preoperative value and two at 24 h. NfL, tau, NSE and S100B increased significantly when 24 h concentrations were compared with preoperative values. However, GFAP concentration did not differ significantly when the 24-h samples were compared to baseline. Interestingly, GFAP exhibited a nonsignificant trend towards decrease at both the 2- and 24-h samples compared to baseline. In addition, NSE showed a nonsignificant decrease in the 2-h sample, followed by a statistically significant increase in the 24-h sample (see Table 2).

The time-profile of each biomarker is shown in the boxplots in Figures 1a, 1b, 1c, 1d, and 1e.

3.3. Patient Positioning. Most patients, $n = 17$, had surgery in the Trendelenburg position; $n = 6$ patients had surgery in the supine position. Positioning was determined by the surgical procedure and was not influenced by the study protocol. Shortly after induction and endotracheal tube placement, the patients scheduled for surgery in the Trendelenburg position were tilted head down, 25°–30°, a position which was maintained until the completion of the surgery.

TABLE 2: Levels of brain injury biomarkers.

pg/mL median (IQR)	Preoperatively	2 h	24 h	*p*
NfL	13.0 (9.5)	13.0 (11.4)	20.4. (13.7)	< 0.001
tau	5.8 (3.6)	7.4 (5.4)	7.6 (3.4)	0.005
NSE	10,750 (3870)	10,100 (4520)	12,350 (12700)	< 0.001
S100B	30.0 (30.0)	139.0 (122.0)	68.0 (57.0)	< 0.001
GFAP	123 (91.1)	99.8 (88.3)	109.5 (106.8)	0.058

Abbreviations: GFAP, glial fibrillary acidic protein; h, hours; IQR, interquartile range; mL, millilitre; NfL, neurofilament light; NSE, neuron-specific enolase; Pg, picogram; S100B, calcium-binding protein S100beta (S100B).

Sensitivity analyses were performed separately on patients in Trendelenburg and supine positions (see Table 3). Brain injury biomarkers in blood demonstrated a statistically significant increase regardless of patient position for NfL and S100B, but only in the Trendelenburg position for NSE and tau. Levels of GFAP remained unchanged regardless of patient positioning.

3.4. Blood Pressure and Cerebral Oxygenation (NIRS) During Anaesthesia and Surgery. There was no significant decline in the MAP or NIRS during anaesthesia and surgery for any of the patients. The continuous arterial blood pressure had a mean of 83.5 mmHg, a range of 62.2–90.4 mmHg, and no patient had a drop in MAP of 20% or more compared to preanaesthesia values. The mean NIRS was 77.5% (range 62.2–90.4). No patient had a drop in NIRS of 12% or more.

3.5. Postoperative Follow-Up. Patients were followed up for 48 h or until discharge. Postoperative symptoms of confusion or neurological deficits were not observed in any patient within 48 h from the start of anaesthesia. Respiratory complications, such as mild hypoxia (pulse oximeter of 94%–95%), gathering one point in NEWS2, occurred in 35% of patients during the postoperative period. No surgical complications were observed. No hypotensive episodes were noted; two patients had a temperature of > 38°C within the observation period, rendering one point in NEWS2.

4. Discussion

This study examined brain injury biomarkers in patients undergoing uneventful anaesthesia and noncerebral surgery. During the intervention, all patients had well-maintained physiological parameters, such as blood pressure and NIRS, and displayed no postoperative signs of cerebral hypoperfusion. In this cohort, levels of NfL, tau, NSE and S100B were statistically significantly increased after 2- and 24-h periods compared to preoperative levels. Furthermore, there was no statistically significant change in the levels of biomarker

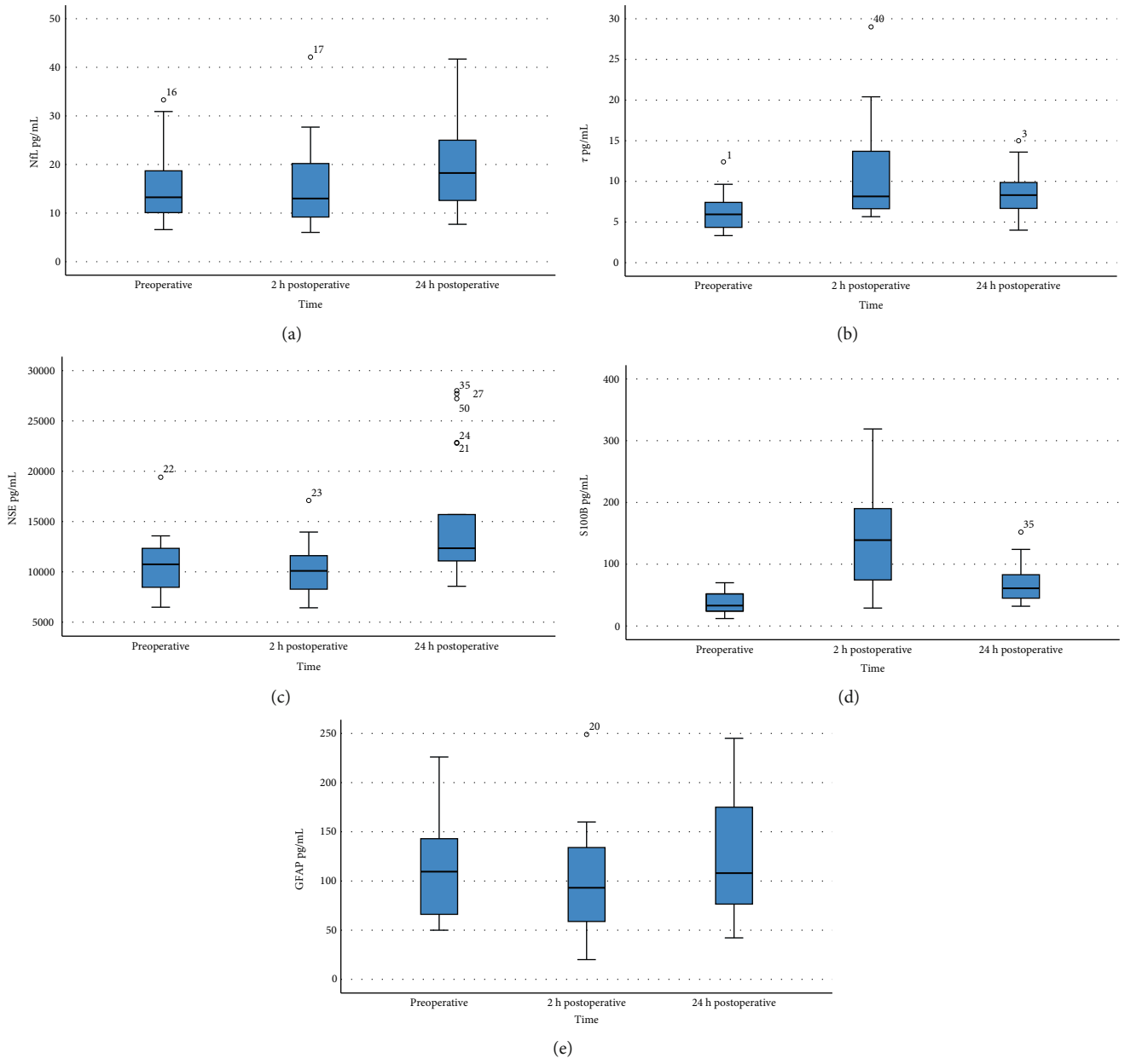

FIGURE 1: (a–e) Boxplots displaying trajectory over time for the concentrations of each biomarker.

GFAP when comparing preoperative and postoperative levels.

The trajectory of biomarker increase in the absence of postoperative clinical neurological symptoms suggests that extracranial sources, such as peripheral nerve or tissue injury, may contribute to their release [26–30]. However, a cerebral origin cannot be ruled out, since mild or subclinical neuronal damage may not manifest as overt dysfunction. Another plausible explanation may be variations in the clearance of biomarkers by the glymphatic system, activated during anaesthesia [31]. This is further discussed below.

An increase of brain injury biomarkers in blood during anaesthesia and noncerebral surgery has previously been reported for NfL and tau [11]. However, that study did not assess postoperative neurological outcomes. Barbu et al. investigated the abovementioned biomarkers during cardiac surgery and found that all biomarkers were increased without signs of blood-brain barrier damage [32]. However, these patients were on cardiopulmonary bypass, possibly influencing biomarker release [33].

In a study by Andersson et al. [34], S100B was increased in trauma patients without evident head injury.

In another study, investigating marathon runners, serum S100B was elevated after the race despite participants showing no symptoms or signs of cerebral injury. The rise in S100B correlated strongly with increased creatine kinase (CK) levels, suggesting that the S100B originated from extracranial sources, likely muscular tissue. Notably, GFAP levels remained unchanged, further supporting the conclusion that the elevated S100B did not reflect glial or brain damage [35].

TABLE 3: Sensitivity analysis on patient positioning.

pg/mL median (IQR)	Preoperatively	2 h	24 h	*p*
NfL TBG	12.4 (5.2)	14.0 (11.7)	21.1 (14.1)	0.001
NfL SUP	17.8 (82.6)	16.1 (17.3)	19.9 (75.8)	0.016
tau TBG	5.4 (3.6)	6.8 (3.3)	7.8 (2.8)	0.024
tau SUP	8.0 (8.4)	17.8 (29.5)	10.5 (18.6)	0.3
NSE TBG	10,390 (4570)	10,305 (4650)	12,555 (6630)	0.003
NSE SUP	11,900 (5130)	10,565 (3680)	12,150 (14300)	0.115
S100B TBG	32.0 (40.0)	136 (100)	52.0 (40.0)	0.001
S100B SUP	31.5 (30.0)	201 (200)	94.0 (90.0)	0.006
GFAP TBG	110 (86.4)	89.1 (59.8)	110 (82.8)	0.062
GFAP SUP	134 (113)	148 (135)	134 (112)	0.607

Abbreviations: GFAP, glial fibrillary acidic protein; h, hours; IQR, interquartile range; mL, millilitre; NfL, neurofilament light; NSE, neuron-specific enolase; Pg, picogram; S100B, calcium-binding protein S100beta (S100B); SUP, supine position; TBG, Trendelenburg position.

These data support that the S100B can be released from damaged extracranial soft tissues into the bloodstream, which means the actual surgery or the anaesthesia might have induced the increase of S100B in our study.

The time profile is different for each of the biomarkers; for example, S100B is rapidly released after injury and has its expected peak within the first hours after injury, and then, it is cleared from blood. In our study, it peaks at 2 h and then decreases to 24 h, which is to be expected [36].

In our data set, NSE initially decreased between preoperative values and 2 h, postoperatively. We do not know the reason for this; it may be due to haemodilution, but this is mere speculation. NSE increased to 24 h, postoperatively, but with a large increase in IQR as well. The dataset for NSE at 24 h had several outliers (> 2 SD but < 3 SD) with high values. It is possible that the abundance of outliers was caused by ruptured blood cells, caused by the surgery itself.

In our study, NfL and tau both have a slower and steadier increase over time than S100B and GFAP and had fewer outliers than NSE. As they are both prevalent in peripheral nerves that may get damaged during surgery, these results are difficult to interpret in a surgical setting. Furthermore, as tau is also prevalent in abdominal organs, it may be unsuitable for patients undergoing abdominal surgery.

Although not statistically significant, there was a tendency towards decreased levels of GFAP in our study; the reason for this remains unknown. However, one might speculate that whilst the impact of haemodilution on levels of brain injury biomarkers in blood is difficult to quantify, the unchanged levels of GFAP could possibly be caused by dilution, masking a minor release. Nonetheless, it is notable that all other analysed biomarkers also demonstrated increases despite the same dilutional context.

According to previous data, GFAP levels increase already 1 h after injury and peak at 20 h after traumatic brain injury, an ischemic insult or a period of hypoxic hypoperfusion, meaning it was measured in this study at time points where an increase would have been detected [37, 38]. To our knowledge, GFAP has only been demonstrated to increase in blood levels during anaesthesia and noncerebral surgery in the study from Barbu et al. [32], where an increase of 17% was demonstrated in patients undergoing cardiac surgery with cardiopulmonary bypass. Contrary to this, our results suggest that anaesthesia and noncerebral surgery with well-maintained vital parameters perioperatively do not cause elevated levels in plasma concentration of GFAP and that GFAP, in fact, is unaffected by general anaesthesia and surgery. Previous reports support this finding [39].

Currently, several of the brain injury biomarkers studied here are used in clinical practice for prognostication and diagnostics, to aid clinical decision-making. For example, NSE and NfL are used for prognostication after cardiac arrest and stroke, respectively, and S100B is used to assess the degree of brain injury after head trauma such as concussions [6, 7, 11, 40]. Recently, GFAP was also suggested as the most accurate biomarker to assess head trauma [41]. Our data should not be interpreted as invalidating the use of NfL, tau, NSE or S100B for prognostication in cases of suspected brain injury. However, in patients undergoing anaesthesia and surgery without clinical signs of cerebral insult, elevations may arise from other mechanisms and could lead to overestimation of injury severity if not considered carefully. Previous studies have demonstrated that sedation and anaesthesia do not adversely affect the prognostic performance of these biomarkers in cardiac arrest patients, and this should be taken into account when interpreting the clinical significance of postoperative elevations [42–48]. If it is unclear to what extent anaesthesia and surgery contribute to the release of brain injury biomarkers into the blood, results may be overinterpreted. Our results further add to the body of evidence that the investigated biomarkers are released during anaesthesia and surgery. We cannot from this study state, with certainty, whether the source of this release is from intracranial or extracranial origin.

4.1. Patient Positioning—Sensitivity Analyses. Most patients in our study cohort had surgery in the Trendelenburg position. It has been reported that the Trendelenburg position per se can cause cerebral venous stasis and affect cerebral perfusion. However, reports are nonconclusive, and this

position is widely used and considered safe by most reports [49–51]. A sensitivity analysis of our data demonstrated that tau and NSE levels were not significantly increased in patients undergoing surgery in the supine position but only in the Trendelenburg position. S100B and NfL levels significantly increased in both the supine and the Trendelenburg position. Notably, GFAP was the only biomarker unaffected by anaesthesia and surgery regardless of patient positioning.

Our study cannot explain the underlying reasons for the incoherent results in biomarker release. However, there is growing evidence that cerebrospinal fluid clearance of brain injury biomarkers is posture-dependent. For instance, glymphatic flow is most effective in the lateral recumbent position and significantly reduced in head-down or prone positions [52]. It is plausible that biomarker accumulation postoperatively, particularly for tau and NfL, may in part be influenced by altered glymphatic or lymphatic clearance in the Trendelenburg position [53, 54].

4.2. Strengths and Limitations. Data was collected in an authentic clinical setting, with mixed abdominal surgical patients having procedures as per hospital protocol. As the study aimed to find a brain injury biomarker unaffected by anaesthesia and surgery, this provided a robust setting. All patients were extensively monitored with particular attention to blood pressure and cerebral oxygenation throughout the study. Patients followed a standardised protocol for patient care, blood sampling and follow-up. Blood samples were analysed in an accredited laboratory which routinely performs brain-injury biomarker analyses.

This is a single-centre study, and the small study sample limits the generalisability of the data. The investigated population is heterogeneous regarding surgical procedures, duration of surgery and supplementary drugs, but it enables the identification of a robust biomarker unaffected by any general anaesthesia, interventions and surgical procedures.

To monitor cerebral perfusion, we used NIRS, which measures cerebral oxygenation as a surrogate. A limitation of this technique is that NIRS only measures oxygenation in the tissues close to the attached electrodes and not in the whole brain.

Our study used NEWS2 as follow-up after surgery, in accordance with hospital protocol. This is a rather blunt instrument, especially for detecting cognitive dysfunction. Furthermore, this study was limited to 48-h follow-up, and a more extended study period may have yielded different results. However, it could be argued that even with this short time-span, major neurological impairment caused by surgery and anaesthesia would be evident.

5. Conclusion

In this study, general anaesthesia and noncerebral surgery in patients with well-maintained cerebral perfusion caused an increase in the brain injury biomarkers NfL, tau, NSE and S100B in blood. However, there was no change in levels of blood GFAP in this cohort, suggesting that the release of GFAP is unaffected by general anaesthesia and noncerebral surgery, thus holding the potential as the most relevant cerebral-specific biomarker of those analysed in this setting. However, our findings underscore the complexity in the interpretation of biomarker elevations in the perioperative setting and highlight the need for context-aware interpretation when using these biomarkers in the perioperative period.

More extensive studies on this subject are warranted.

Data Availability Statement

Unidentified data can be provided upon reasonable request.

Ethics Statement

The study was approved by the Swedish Ethical Review Authority (Dnr 2020-00169) on 10-03-2020, and the protocol adheres to the latest version of the Declaration of Helsinki. Signed informed consent was obtained for all patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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