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RESEARCH ARTICLE

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Hypotension during transsphenoidal pituitary surgery associated with increase in plasma levels of brain injury markers

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Abstract

Background: Patients undergoing pituitary surgery may experience short- and long-term postoperative morbidity. Intraoperative factors such as hypotension might be a contributing factor. Our aim was to investigate the association between intraoperative hypotension and postoperative plasma levels of tau, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) as markers of perioperative brain injury.

Methods: Between June 2016 and October 2017, 35 patients from the Gothenburg Pituitary Tumor Study were included. For tau, NfL, and GFAP, concentrations were measured in plasma samples collected before and immediately following surgery, and on postoperative days 1 and 5. The difference between the highest postoperative value and the value before surgery was used for analysis (Δtau_{peak}, ΔNfL_{peak}, $\Delta GFAP_{peak}$). Intraoperative hypotension was defined as the area under the curve of an absolute threshold below 70 mmHg (AUC70) and a relative threshold below 20% (AUC20%) of the baseline mean arterial blood pressure.

Thomas Skoglund and Jonatan Oras are contributed equally to this study.

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Results: Plasma tau and GFAP were highest immediately following surgery and on day 1, while NfL was highest on day 5. There was a positive correlation between AUC20% and both Δtau_{peak} ($r^2 = .20$, $p < .001$) and ΔNfL_{peak} ($r^2 = .26$, $p < .001$). No association was found between AUC20% and GFAP or between AUC70 and Δtau_{peak}, ΔNfL_{peak} or $\Delta GFAP_{peak}$.

Conclusion: Intraoperative relative, but not absolute, hypotension was associated with increased postoperative plasma tau and NfL concentrations. Patients undergoing pituitary surgery may be vulnerable to relative hypotension, but this needs to be validated in future prospective studies.

KEYWORDS
biomarkers, hypotension, neurosurgery, pituitary tumors

Editorial Comment

Patients undergoing pituitary surgery under general anesthesia are at risk of postoperative brain injury, which may be due to the direct effect of general anesthetics, physiological aberrations such as hypotension, and direct mechanical injury during surgery. This study examined the relationship between intraoperative hypotension and postoperative change in three markers of brain injury: glial fibrillary acidic protein (GFAP), tau, and neurofilament light, in adults undergoing pituitary surgery. Intraoperative hypotension measured as >20% reduction from baseline mean arterial pressure was associated with the peak increase in tau and GFAP. Still not understood is if these relations are causal, specific for pituitary surgery, or more general in nature.

1 | INTRODUCTION

There is increasing evidence linking brief periods of intraoperative hypotension (IOH) to postoperative myocardial and kidney injury,[1] and increased mortality.[2] However, a controversy exists regarding the effects of IOH on perioperative neurological injury, such as neurocognitive disorders and stroke, with conflicting results appearing in previous studies.[3–5]

During neurosurgical procedures, several factors might increase vulnerability to hypotension resulting in brain injury. Brain tumors can negatively affect the autoregulatory capacity of the cerebral circulation and hence tolerance to episodes of hypotension.[6] Moreover, the manipulation of brain tissue, which commonly occurs during neurosurgical procedures, could further compromise brain perfusion and vulnerability to hypotension.[7]

Although surgery for pituitary tumors performed through the transsphenoidal route is generally considered a procedure with a low risk of neuronal injury, mechanical manipulation, direct injury, and compromise of perfusion to the posterior lobe may lead to injury.[8] Furthermore, manipulation of suprasellar neuronal structures is sometimes also unavoidable. Importantly, it has been proposed that the surgical procedure itself could be partly responsible for poor outcomes,[9] which in turn might indicate that manipulation of these structures during surgery may precipitate such neuronal injury.[8]

Following both neurological and non-neurological surgery, there is an increase in circulating levels of the brain injury biomarkers tau, glial fibrillary acidic protein (GFAP), and neurofilament light (NfL).[8,10–13] Only one previous study has investigated the association between IOH and biomarkers of brain injury in neurosurgery. In that study, an association was found between IOH and an increase in neuron-specific enolase (NSE) in skull base surgery following deliberate hypotension.[14]

Since hypotension may increase vulnerability to surgical manipulation and since IOH has been associated with elevated postoperative levels of brain injury biomarkers following neurological surgery, it is possible that this could be a contributing mechanism to brain injury following pituitary surgery. Therefore, this study aimed to test the hypothesis that the degree and duration of intraoperative hypotension during pituitary surgery were associated with increased plasma concentrations of the brain injury biomarkers tau, GFAP, and NFL.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a secondary analysis of data reported in the Gothenburg Pituitary Tumor (GoPT) study that prospectively enrolled consecutive patients scheduled for elective pituitary surgery.[15] The study was approved by the Regional Ethics Review Board in Gothenburg, Sweden (Dnr: 387-15, 6/20/2015) and registered on Researchweb.org with International Registered Report Identifier (IRRID): DERR1-10.2196/17696. Patients >18 years of age were consecutively enrolled between June 2016 and October 2017. Written

informed consent was obtained from all participants prior to inclusion. All patients subsequently underwent endoscopic transsphenoidal resection of their pituitary tumor.

2.2 | Analysis of biomarkers

Blood was sampled in EDTA-containing tubes preoperatively, immediately following surgery, and on postoperative days 1 and 5. The samples were promptly centrifuged for 10 min, and 1 mL plasma aliquots were subsequently stored at −70°C before being transported to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital Mölndal, Sweden, for analysis. The result of measuring biomarkers in this cohort have been presented in a previous study where we demonstrated that GFAP and tau had peak levels either immediately following surgery or on day 1, whereas NfL continued to increase up to day 5 (Supplementary Information 1).[8]

Plasma concentrations of total tau (t-tau) and GFAP were measured using commercially available digital enzyme-linked immunosorbent assay (ELISA) kits (targeting the mid-region of tau and the central alpha-helical rod of GFAP, respectively) on the Single molecule array (Simoa) HD-1 analyzer (Quanterix, Billerica, MA, USA) following the manufacturer's instructions. Plasma NfL concentration was measured using an in-house assay on the Simoa platform, as previously described.[16] The intra-assay coefficients of variation, determined by analyzing duplicate samples for all measurements, were less than 10% for all biomarkers.

To normalize for variations in baseline levels of biomarkers, the difference between the postoperative and the preoperative value was calculated for all measurements. We used the value of NfL on day 5 as the peak value and compared it to baseline NfL (ΔNfL_{peak}), and we took the highest value of tau and GFAP either immediately following surgery (day 0) or on the first day following surgery (day 1) and compared it to baseline (Δtau_{peak} and $\Delta GFAP_{peak}$). Tau and GFAP were analyzed on day 0 in 14 patients, and on day 1 in 32 patients. If either sample on day 0 or day 1 was missing, we used whatever measurement was available as the peak value.

2.3 | Anesthesia

Standard monitoring equipment, including pulse oximetry, electrocardiography, noninvasive blood pressure, and capnography, was used. Following the induction of general anesthesia, invasive blood pressure measurement was established in all patients.

Anesthesia was induced with propofol (1–6 mg/kg) and a plasma-targeted controlled infusion (TCI) of remifentanil (at 6 ng/mL). Following induction, anesthesia was maintained with remifentanil with TCI targeting a plasma concentration of at least 6 ng/mL or fentanyl and either sevoflurane at approximately 0.7 minimal alveolar concentration (MAC), or propofol targeting a plasma concentration of 2–6 mcg/mL at the discretion of the attending anesthesiologist.

Blood pressure was targeted to maintain mean arterial pressure (MAP) >65–75 mmHg in all patients through intravenous bolus doses of ephedrine, phenylephrine, and/or a continuous infusion of norepinephrine. The targeted MAP was decided by the attending anesthesiologist.

2.4 | Data collection

Preoperative data, including patient characteristics, comorbidities, and the duration of anesthesia, were obtained from electronic medical records and included information on any adrenal insufficiency and concomitant glucocorticoid replacement therapy. Comorbidities were classified as present if stated in the medical record or if medication for a specific comorbidity was prescribed to the patient. Intraoperatively, heart rate and blood pressure were measured continuously and recorded every 5 min.

2.5 | Definitions of intraoperative hypotension

To establish resting blood pressure as a reference value, blood pressure was measured on the ward the day before surgery and before induction of general anesthesia. The lowest reading obtained was used as the reference value.

Intraoperative hypotension was defined as the area under the curve of below an absolute threshold below a MAP <70 mmHg (AUC70) and a relative threshold of MAP <20% (AUC20%) of the reference value, expressed as mmHg * min.

To account for the potential effects of surgical trauma on the plasma levels of tau, NfL, and GFAP, we analyzed the association between Δtau_{peak}, ΔNfL_{peak}, $\Delta GFAP_{peak}$, and the degree of hypothalamic and chiasmal compression, as previously described.[8]

2.6 | Statistical analysis

Normally distributed variables are presented as mean ± (standard deviation) and non-normally distributed variables are presented as median (25th–75th percentile). Categorical variables are presented as frequency (percentage).

No previous data on circulating levels of NfL, tau, and GFAP overtime was available in patients undergoing this type of surgery. Power analysis to determine the sample size was therefore not performed.

The prespecified primary outcome was the association between intraoperative hypotension, measured as AUC 20% and AUC 70, and the peak increase in cerebral biomarkers. Due to the skewed distribution of biomarker data and the presence of outliers, we employed in the univariable analysis a non-parametric test using a quantile regression of the median to evaluate variables associated with Δtau_{peak}, ΔNfL_{peak}, $\Delta GFAP_{peak}$. Baseline characteristics, degree of hypothalamic and chiasmal compression, comorbidities, and intraoperative variables including the various definitions of hypotension were included in the

TABLE 1 Patient characteristics and procedural data.

Age (year), median (IQR)	64 (45–74)
Male, *n* (%)	20 (57)
BMI, mean (SD)	28 ± 4
Bleeding (mL), median (IQR)	135 (50–200)
Perioperative fluid balance (mL), median (IQR)	325 (−50 to 650)
Maintenance of anaesthesia, *n* (%)	
Sevoflurane and remifentanil	30 (86)
Propofol and remifentanil	3 (9)
Sevoflurane and fentanyl	2 (6)
Duration of anaesthesia (hours)	4.6 (3.9–4.8)
Duration of surgery (hours)	3.1 (2.3–3.7)
Sevoflurane, MAC, mean (SD)	0.7 (0.1)
Remifentanil, TCI Cpt ng/mL, mean (SD)	6 (0.7)
Propofol, TCI Cpt μg/mL, median (IQR)	4.2 (3.3–4.6)
Norepinephrine, total dose (μg), median (IQR)	783 (555–1306)
Phenylephrine, total dose (μg), median (IQR)	450 (288–625)
Ephedrine, total dose (mg), median (IQR)	20 (15 to 30)
Comorbidities, *n* (%)	
Ischemic heart disease	3 (9)
Ischemic stroke	3 (9)
Diabetes mellitus type II	7 (20)
Hypertension	15 (43)
Heart failure	1 (3)
Preoperative adrenal deficiency, *n* (%)	11 (31)
Chiasmal compression, *n* (%)	
None	7 (20)
Some	5 (14)
More	23 (66)
Hypothalamic compression, *n* (%)	
None	18 (51)
Some	7 (20)
More	10 (29)

Abbreviations: ASA, American Society of Anesthesiologists; Cpt, concentration plasma target; IQR, interquartile range; MAC, minimum alveolar concentration; SD, standard deviation; TCI, targeted controlled infusion.

analysis. No correction for multiple comparisons were made. Correlations with a $p < .1$ were then included in a multivariable analysis. Due to the dependent nature of AUC20% and AUC70, separate multivariable analyses were performed between these variables and other significant univariable correlations.

To further analyze the relationship between relative hypotension and the release of tau and NfL, we divided the patient cohort into two groups, *high* and *low* Δtau_{peak} and high and low ΔNfL_{peak}, respectively, based on whether they were above or below the median value of Δtau_{peak} and ΔNfL_{peak}. The difference in MAP between the high and low groups during the procedure was analyzed using a linear mixed model with an autoregressive covariance matrix. The significance level was set at .05. Statistical analysis was performed using SPSS software (IBM Corp., version 24, Armonk, NY).

3 | RESULTS

A total of 66 patients were included in the parent study during the research period. Among these, blood samples were collected and analyzed for biomarkers in 35 patients. Median bleeding volume was 135 (50–200) mL and most patients ($n = 32$, 91%) were anesthetized with sevoflurane and remifentanil. Ten patients (29%) were in the American Association of Anesthesiologists (ASA) class I, 21 (60%) in ASA II, and 4 (11%) were in ASA class III. The most common comorbidities were hypertension in 15 (43%) and diabetes mellitus in 7 (20%) patients. Most patients ($n = 23$, 66%) had chiasmal compression from the pituitary tumor, whereas half had no hypothalamic compression ($n = 18$, 51%) (Table 1).

Twenty-six patients received norepinephrine infusion, 20 received intermittent phenylephrine, and 22 received intermittent ephedrine to maintain blood pressure.

Following the induction of anesthesia, the mean MAP for the whole cohort decreased from 94 ± 9 mmHg at baseline to 72 ± 10 mmHg after 30 min of anesthesia. For the remaining periods of the procedures, the mean MAP stabilized mean MAP 73 ± 6 mmHg. Mean arterial pressures at 15-min intervals for all procedures are shown in Figure 1.

There was a significant positive correlation between the area under the relative thresholds for hypotension (AUC20%) and Δtau_{peak} ($r^2 = .20$, $p < .001$) and ΔNfL_{peak} ($r^2 = .26$, $p < .001$) (Figure 2). There was no association between AUC20% and GFAP ($r^2 = .03$, $p = .18$), and no association between the absolute thresholds of MAP 70 mmHg (AUC70) and Δtau_{peak} ($r^2 = 0.02$, $p = .21$), ΔNfL_{peak} ($r^2 = .05$, $p = .25$), or $\Delta GFAP_{peak}$ ($r^2 = .01$, $p = .67$) (Table 2).

The median Δtau_{peak} was 0.2 (−0.7 to 1.2) pg/mL. The relative MAP (expressed as a % of baseline MAP) was lower in the *high* Δtau_{peak} group as compared to the low Δtaupeak group (76% ± 11% vs. 83% ± 9% vs., $p < .001$). The median ΔNfL_{peak} was 6.20 (4.2–13.8) pg/ml. Similarly, the relative MAP (expressed as a % of baseline MAP) was lower in the *high* ΔNfL_{peak} group compared to the low ΔNfL_{peak} group (77% ± 11% vs. 82% ± 11% vs., $p < .001$) (Supplementary Information 2).

No association was found between Δtau_{peak}, ΔNfL_{peak}, $\Delta GFAP_{peak}$, duration of surgery, duration of anesthesia, blood loss, the total dose of norepinephrine, the median concentration of sevoflurane, the median concentration of remifentanil, degree of tumor compression of hypothalamus or chiasma, adrenal insufficiency, patient age, diabetes mellitus, or chronic hypertension. No analysis was done on the anesthetic doses of the three patients anesthetized with propofol and remifentanil due to the small number of patients. There was an association between previous ischemic stroke and Δtau_{peak} (Table 3). In the multivariable analysis, both AUC20% and previous ischemic stroke remained significantly associated with Δtau_{peak} ($r^2 = .34$, $p < .001$) (Supplementary Information 3).

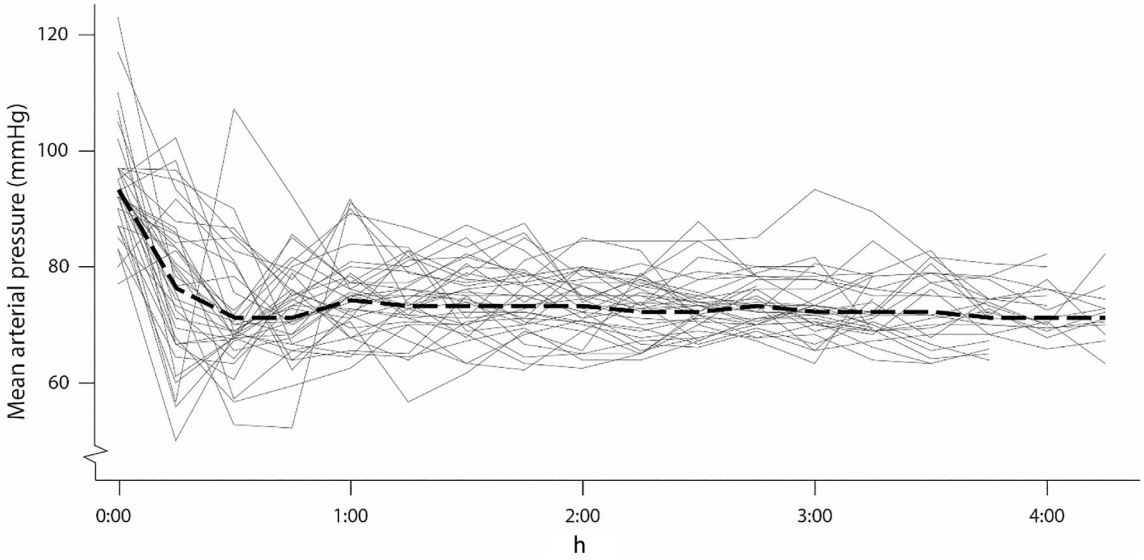

FIGURE 1 Intraoperative MAP values. Individual MAP values ($n = 35$) are plotted at 15-min intervals for the first 4 hours of surgery. The value plotted is the mean value during the time period. The mean of all measurements at every interval is indicated by the bold line. Reference MAP is shown at the first measurement. Reference mean MAP for the whole cohort was 94 ± 9 mmHg and decreased to 72 ± 10 mmHg after 30 minutes of anesthesia. For the remainder of the procedures, mean MAP was 73 ± 6 mmHg. MAP, mean arterial pressure.

4 | DISCUSSION

The primary finding of this study was an association between relative intraoperative hypotension, defined as the area under a threshold value of MAP below 20% of the reference value, and postoperative release of the brain injury biomarkers tau and NfL in patients undergoing transsphenoidal pituitary surgery.

Studies evaluating the outcome of patients with pituitary tumors following surgical resection are equivocal regarding the long-term effects on health-related quality-of-life (HRQoL).[17,18] Symptoms such as fatigue and cognitive impairment, have been reported, and it is possible that surgical and anesthesiologic factors may be contributing to these issues.[9] Therefore, identifying intraoperative factors that may be responsible for poor outcomes following pituitary surgery have important clinical consequences. Our results suggest that intraoperative hypotension may be an intraoperative factor that might influence clinical outcomes.

Only a few studies have investigated the association between comorbidities and intraoperative factors on the postoperative release of brain injury biomarkers. Wiberg and colleagues randomized patients to high versus low MAP during cardiac surgery and found no difference in biomarkers between the two groups.[19] Moreover, Ballweg and colleagues included hypotension as a covariate in a multivariable linear regression model of clinical predictors of both tau and NfL following major surgery in a study on the association between delirium, biomarkers of neuronal injury and inflammation following noncardiac and non-intracranial surgery and found an association with age, previous transient ischemic attack or cerebrovascular insult and blood loss but no association with hypotension.[20] To our knowledge, there is only one previous study that has studied the impact of hypotension on biomarker release during intracranial surgery. In this study, deliberate hypotension was associated with increased levels of the brain injury biomarker neuron-specific enolase.[14]

Our data suggest that patients undergoing pituitary surgery may have an increased sensitivity to intraoperative hypotension. However, given the scarcity of the available evidence on the relationship between intraoperative hypotension and postoperative levels of brain injury biomarkers, whether our findings are relevant for pituitary surgery alone, intracranial surgery more generally, or for extracranial surgery as well, remains to be elucidated.

An important confounder between the association of brain injury biomarkers and IOH is the complexity of the surgery. Both surgical complexity and longer duration of surgery are likely to result in more time below a blood pressure threshold that ensures adequate cerebral perfusion and more severe bleeding could be associated with greater hemodynamic instability. For that reason, we analyzed these variables and their impact on biomarker release but were not able to find any such associations. We did however find that previous ischemic stroke was associated with postoperative tau release and both intraoperative hypotension and previous ischemic stroke were significantly associated with tau release in the multivariable regression analysis. Interestingly, this association has previously been described by Ballweg and colleagues.[20] The risk of major adverse cardiovascular events and mortality following surgery in patients who have had a previous ischemic stroke has previously been shown to be increased.[21] This finding could indicate an increased vulnerability to further brain injury in this subgroup of patients more likely to have arteriosclerosis in the brain or its supporting arteries.

In the present study, we only found a correlation between the relative, and not the absolute threshold and tau and NfL. Episodes of IOH below the absolute threshold of 70 mmHg were uncommon in

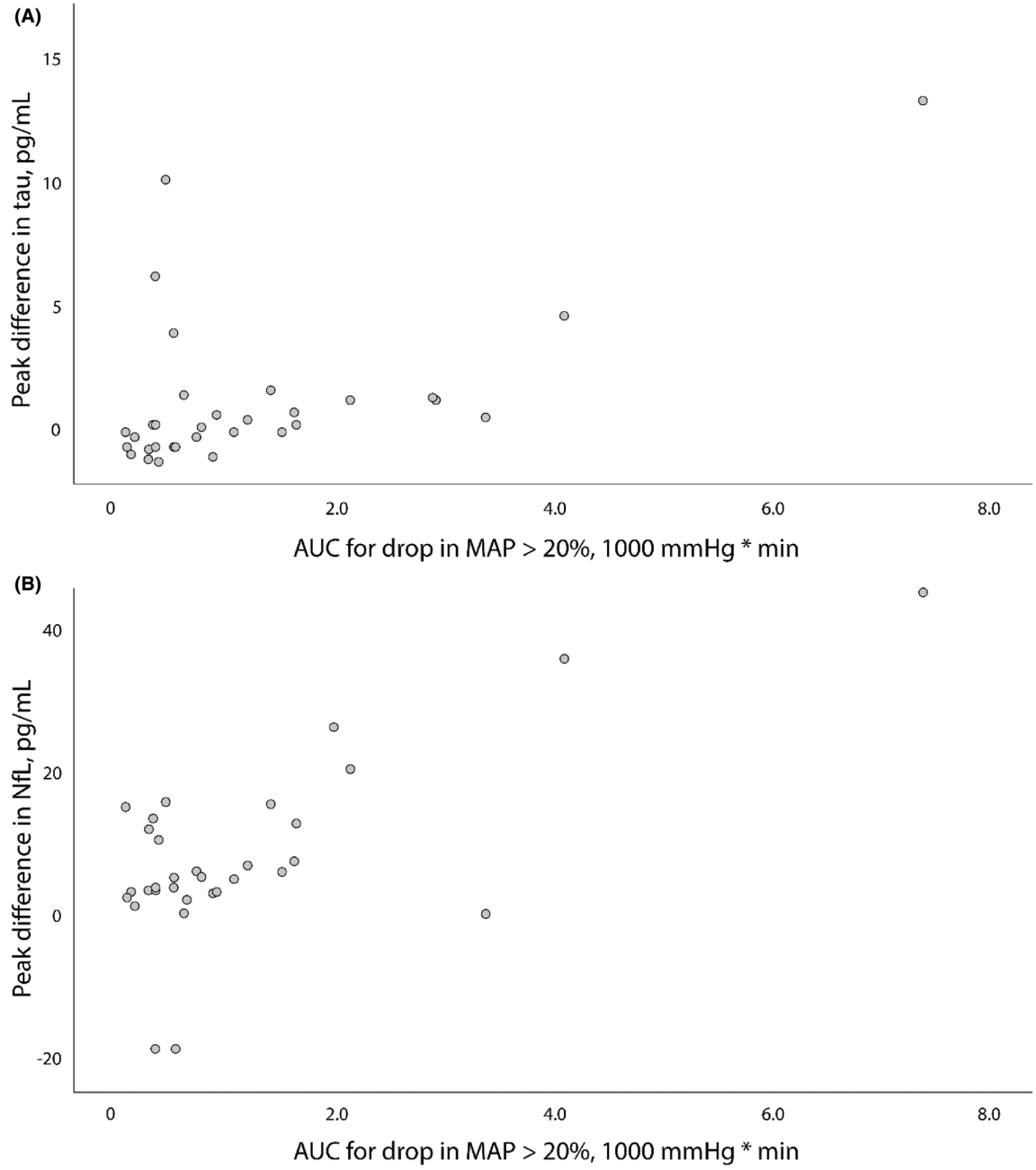

FIGURE 2 Scatterplot for the difference between preoperative and peak value of tau (A) and NfL (B) plotted against the AUC for a decrease in MAP of 20% or more from the reference MAP (AUC20%). The correlation coefficient using quantile regression analysis for tau and AUC20% was $r^2 = .20$ ($p < .001$) and for NfL $r^2 = .26$ ($p < .001$). AUC, area under the curve; MAP, mean arterial blood pressure; NfL, neurofilament light.

the population we studied as compared with the significantly higher relative MAP threshold level where a 20% decrease in MAP (AUC20%) resulted in a mean threshold MAP of 76 mmHg. This implies that the risk of injury due to IOH increases at higher blood pressure threshold values than 70 mmHg during pituitary surgery. We were able to show that those patients having a higher increase in tau and NfL (i.e., patients in the upper median) had a more pronounced decrease in reference MAP than patients with less of an increase. This further emphasizes that the relative blood pressure drop was more important in this cohort and that the accumulated "dose" of hypotension seems to be of greater significance than single episodes of hypotension.

There was no association between GFAP, which origin is glial cells, and IOH. This could be one possible reason for the lack of association as glial cells are more resilient to the effects of hypotension than neurons (tau) and axons (NfL).

Our study has several limitations that should be addressed. First, it was a post hoc analysis of a prospective study describing the release pattern of tau, NfL, and GFAP following pituitary surgery, and was not originally designed to test the impact of hypotension on the release of

TABLE 2 Association between hypotension and peak increase in tau, NfL, and GFAP compared to baseline.

	Univariable regression				
			95% CI for coefficient		
Dependent variable	Coefficient	r^2	Lower limit	Upper limit	*p*
Relative threshold AUC20%					
Δtau_{peak}	1.1	.20	.8	1.4	<.001
ΔNfL_{peak}	5.9	.26	3.5	8.3	<.001
$\Delta GFAP_{peak}$	38.1	.03	−18.1	94.3	.18
Absolute threshold AUC70					
Δtau_{peak}	1.7	.02	−.9	4.0	.21
ΔNfL_{peak}	7.8	.05	−5.6	21.3	.25
$\Delta GFAP_{peak}$	88.2	.01	−322.6	50.0	.67

Note: Univariable quantile regression analyses were performed with a relative threshold (AUC20%) and absolute threshold (AUC70) as independent variables and Δtaupeak, ΔNfLpeak, and ΔGFAPpeak as dependent variables, respectively. Unit is per 1000 mmHg * minute for all analyses.
Abbreviations: CI, confidence interval; GFAP, glial fibrillary acidic protein; NfL, neurofilament light.

TABLE 3 Clinical and intraoperative variables and association with peak increase in tau, NfL, and GFAP compared with baseline.

	Univariable regression				
			95% CI for coefficient		
Dependent variable	Coefficient	r^2	Lower limit	Upper limit	*p*
History of ischemic stroke					
Δtau_{peak}	9.9	.17	7.9	11.9	<.001
ΔNfL_{peak}	11.2	.10	−2.1	24.5	.10
$\Delta GFAP_{peak}$	77.6	.01	−235.1	390.3	.62
Age, per year					
Δtau_{peak}	.0	.04	−.0	.1	.21
ΔNfL_{peak}	.0	.01	−.2	.3	.70
$\Delta GFAP_{peak}$	2.4	.01	−2.9	7.7	.36
Bleeding, per mL					
Δtau_{peak}	.0	.00	.0	.0	>.999
ΔNfL_{peak}	.0	.00	.0	.0	.28
$\Delta GFAP_{peak}$	.4	.01	−0.2	.9	.16
Duration of surgery, per minute					
Δtau_{peak}	.0	.00	.0	.0	>.999
ΔNfL_{peak}	.0	.05	.0	.0	.32
$\Delta GFAP_{peak}$	−.6	.00	−2.2	1.1	.51
Norepinephrine					
Δtau_{peak}	.0	.00	.0	.0	>.999
ΔNfL_{peak}	.0	.10	.0	.0	.12
$\Delta GFAP_{peak}$	−.3	.00	−.2	.1	.68
Duration of anaesthesia, per minute					
Δtau_{peak}	.0	.00	.0	.0	>.999
ΔNfL_{peak}	.0	.04	.0	.1	.44
$\Delta GFAP_{peak}$	−.5	.00	−1.7	.7	.42
Hypothalamic compression					
Δtau_{peak}	.0	.00	−1.3	1.3	>.999
ΔNfL_{peak}	−0.2	.00	−7.6	7.2	.96

(Continues)

TABLE 3 (Continued)

	Univariable regression				
			95% CI for coefficient		
$\Delta GFAP_{peak}$	97.1	.03	−80.9	275.1	.28
Chiasma compression					
Δtau_{peak}	.5	1.70	−.9	1.9	.48
ΔNfL_{peak}	−3.1	.01	−11.9	5.7	.48
$\Delta GFAP_{peak}$	76.4	.01	−106.6	259.4	.40
Adrenal insufficiency					
Δtau_{peak}	.0	.00	−1.3	1.3	>.999
ΔNfL_{peak}	−2.7	.02	−11.6	6.2	.54
$\Delta GFAP_{peak}$	−65.5	.01	−249.3	118.3	.47
Diabetes					
Δtau_{peak}	.0	.00	−1.6	1.6	>.999
ΔNfL_{peak}	.9	.00	−8.1	9.9	.84
$\Delta GFAP_{peak}$	.0	.00	−230.3	230.3	>.999
Hypertension					
Δtau_{peak}	.1	.00	−1.2	1.4	.87
ΔNfL_{peak}	−5.5	.00	−13.9	2.9	.19
$\Delta GFAP_{peak}$	54.6	.01	−135.3	244.5	.56
Heart failure					
Δtau_{peak}	.5	.01	−3.2	4.2	.79
ΔNfL_{peak}	−0.9	.00	−22.5	20.7	.93
$\Delta GFAP_{peak}$	−49.6	.00	−567.8	468.6	.84
Sevoflurane (mean MAC)					
Δtau_{peak}	−6.0	.11	−15.3	3.3	.19
ΔNfL_{peak}	−16.6	.00	−53.0	20.0	.35
$\Delta GFAP_{peak}$	−171.1	.00	−920.2	577.9	.64
Remifentanil (mean TCIp)					
Δtau_{peak}	.0	.00	−4.5	4.3	.96
ΔNfL_{peak}	.0	.02	−3.4	1.5	.43
$\Delta GFAP_{peak}$	12.0	.01	−49.3	73.2	.69

Note: A quantile regression of the median was used to evaluate variables associated with Δtau_{peak}, ΔNfL_{peak}, $\Delta GFAP_{peak}$. Unit is per 1000 mmHg * minute for Δtau_{peak}, ΔNfL_{peak} and $\Delta GFAP_{peak}$. The value 0 represents a value less than <.01.
Abbreviations: GFAP, Glial fibrillary acidic protein; MAC, minimum alveolar concentration; NfL, Neurofilament light; TCIp, targeted controlled infusion of plasma concentration.

biomarkers. Furthermore, it has not been established when tau, GFAP, and NfL reach their potential peak values following surgery. Measurements of biomarkers following traumatic brain injury suggest that peak tau and GFAP concentrations occur during the first few days after the injury, whereas the NfL peak likely occurs after several weeks.[22,23] Therefore, the actual peak value may have been missed due to the timing of our sampling. Although all patients had a preoperative baseline measurement of tau, NfL, and GFAP, we were not able to collect samples on all patients *both* immediately after surgery and on day 1. Both these circumstances would have led to higher peak values than those registered.

A possible confounder that may influence perioperative brain injury is the depth of anesthesia. Although controversial, excessive depth of anesthesia has been linked to postoperative delirium,[24,25] which in turn may be linked to elevated postoperative tau and NfL.[20,26] In the present study, we found no association between the depth of anesthesia and biomarker levels. Data on propofol and remifentanil targeted controlled infusion concentrations as well as end-tidal sevoflurane concentration were collected to indicate depth of anesthesia. We cannot rule out an effect of depth of anesthesia on the biomarker release, but a significant effect is less likely, given the lack of association in our analysis.

The lowest value of MAP either obtained before induction of general anesthesia or from the ward the day before surgery was used as the reference blood pressure. This measurement may not adequately represent the reference value as blood pressure is subject to

circadian variation, and other factors that temporarily might influence the blood pressure.[27,28]

Since no data on clinically-relevant neurocognitive outcomes (e.g., postoperative delirium or delayed neurocognitive recovery) were available, no inferences on an association between the postoperative increase in tau and NfL and these outcomes could be made. However, both postoperatively increased NfL and tau have been associated with postoperative delirium suggesting that a postoperative increase in these biomarkers is associated with relevant clinical outcomes.[18,22] Another limitation of the study was the small sample size and multiple analyses, which increased the chance of incidental findings.

Future studies on IOH and biomarker evidence of brain injury in patients undergoing transsphenoidal pituitary surgery are needed given the limitations and small sample size of this study. Furthermore, future efforts should be directed toward investigating other anesthesia-related factors (such as depth of anesthesia) and patient-related factors (such as previous ischemic stroke/TIA) associated with biomarker release in patients undergoing both neurological and non-neurological surgery.

5 | CONCLUSION

This study indicates that patients undergoing pituitary surgery may be vulnerable to relative hypotension. Blood pressure control targeting relative thresholds might be beneficial in reducing perioperative neurological injury in such patients, but this needs to be evaluated in future prospective studies with a prespecified hypothesis on IOH and outcome.

AUTHOR CONTRIBUTIONS

Study concept and design: MT, KB, TH, GJ, DSO, TS, HZ, and JO; data collection: MT, TH, and TS; data analysis and interpretation of results: MT, TS, and JO; manuscript draft: MT, JO, and TS. All authors reviewed and revised the drafted manuscript and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Martin Thorsson, upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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