Scientific paper

Optimised Anaesthesia in Abdominal Cancer Surgery does Not Prevent Increase in Biomarkers of Neuroinflammation

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Abstract

Neurocognitive decline during the perioperative period represents a risk of significant complications, including dementia and death. The aim of our study was to observe the change in biomarkers of neuroinflammation in optimized anesthesia without clinical signs of perioperative neurocognitive decline. Observational study included high-risk surgical patients who underwent large intestinal resections. Balanced anaesthesia was used to maximize cerebral protection. The release of NSE, protein S-100, matrix metalloproteinase-9 (MMP-9) and other biomarkers of cerebral injury were measured in serum samples using immunochemical methods during and after surgery. Profiles of proteins MMP-9 and S-100 showed perioperative increase, which was in accordance with intraoperative cerebral injury. Despite the increase, the S-100 and NSE plasma levels remained within normal range. The study highlights the perioperative expression of proteins MMP-9 and S-100, which might be useful as biomarkers of cerebral injury in the context of balanced anesthesia during major abdominal surgery.

Keywords: Neuroinflammatory biomarkers, fluid optimisation, cognitive dysfunction

1. Introduction

Perioperative neurocognitive decline is a neurocognitive disorder related to the perioperative period.[1] Such patients are at risk of significant complications, including dementia and even death.[2,3] The etiology of postoperative neurocognitive disorder is a polyetiological complication. Endothelial inflammation and subsequent postoperative neuroinflammation can cause neuronal injury. [4–6] Brain biomarkers, such as neuron-specific enolase (NSE) from neurons and neuroectodermal cells and protein S100-B from astroglial and Schwann cells, are commonly released into cerebrospinal fluid and then into the systemic circulation. The release profiles of these biomarkers are different due to hypoxia sensitivity between neurons and astrocytes.5,6

Recent studies confirmed the release of cerebral injury biomarkers, which was caused by neuroinflammation after cardiac surgery (due to microemboli from cardiopulmonary bypass of different types of cerebral injury), and also in some other types of surgery, but the consequences after major abdominal surgery with balanced anesthesia technique have not yet been described.[7,8] An increase in inflammatory biomarkers has been observed after general anesthesia and spinal anesthesia. In particular, cardiac surgery triggers widespread changes in cognition that differ from abdominal surgery, while both surgeries generate substantial acute hippocampal neuroinflammation (i.e., microglial activation) and impairment of neuronal plasticity.[9] In different types of surgery, hippocampal neuroinflammation and behavioral deficits have been reported.[10]

Activated microglia secrete pro-inflammatory factors that can induce astrocyte activation, leading to neuronal death and toxicity, also shown in models of in perioperative neurocognitive disorders of major surgery (e.g., liver surgery).[11] NSE and S100B are already used in clinical practice, clinical significance of other neuroinflammation biomarkers is not yet evaluated.[12,13] Elevated matrix metalloproteinase-9 (MMP-9) levels, similar as NSE and S100B, indicate neuronal damage and correlate with neuroinflammation and acute neurological injuries. [12–14] Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a sensitive marker for neuronal injury, playing a role in protein homeostasis and cellular repair.[15] Glial Fibrillary Acidic Protein (GFAP) reflects astrocytic injury and activation and is widely used to monitor glial responses in neurological disorders.[16] Tau protein and apolipoprotein E (ApoE) are linked to systemic inflammation and neurodegenerative risk.[17,18] In the present study, the release of NSE, protein S-100, GFAP, MMP-9, UCH-L1, tau and apolipoprotein 4 during and after major abdominal surgery was studied. Except for NSE, S-100 and GFAP, these proteins have not been studied before as markers of perioperative neuroinflammation in non-cardiac or non-vascular surgery. apolipo-E4 and UCH- L1 were not studied perioperatively. In our study was observed the perioperative profile of studied proteins with the aim of identify possible laboratory markers of neuroinflammation.

2. Experimental

An observational study was conducted at the University Medical Centre Ljubljana. American Society of Anesthesiologists (ASA) class 2–4 high-risk surgical patients who underwent large intestinal resections were included in the study. Exclusion criteria were underage, pregnant women, laparoscopic surgery, and palliative procedures.

The study was approved by the Slovenian National Medical Ethics Committee. It was registered with ClinicalTrials.gov, Surgical Outcome and Multimodal Monitoring (SOMM) Identifier: NCT02293473. Informed consent was obtained on the day before surgery from all patients.

Dexmedetomidine (As Kalceks, Riga, Latvia) infusion was started (0.5 mcg/kg/hour) on admission and ended after skin suture at the end of the procedure. Before the procedure, the thoracic epidural catheter was inserted in the left lateral position and a test with 3 ml of 2% lidocaine (Fresenius Kabi, Bad Homburg, Germany) was performed. Then, a standard induction to general anesthesia was performed. Anesthesia was maintained by intravenous infusion of propofol (Fresenius Kabi, Graz, Austria). Analgesia was provided by 0.25 % levobupivacaine (Fresenius Kabi, Bad Homburg, Germany) epidurally, with sufentanyl (Hameln Pharma Gmbh, Hameln, Germany) supplementation. 1–2 hours after the epidural bolus of local anesthetic, patient-controlled epidural analgesia with constant infusion rate and additional patient-controlled boluses for postoperative analgesia.

The depth of anesthesia was measured with processed electroencephalogram (EEG) technique (bispectral index (BIS) monitor (BIS XP platform, Aspect Medical Systems, Cambridge, USA)). Baseline values BIS and mean arterial pressure (MAP) were recorded.

The perioperative fluids were optimized according to the hemodynamic values. MAP was maintained within 80% of the baseline values. The depth of anesthesia was adjusted to maintain BIS 40-55. The hemoglobin level was kept above 80 g/L. A decrease in hemoglobin was coping with a blood transfusion. Body temperature was maintained in the range between 36 and 37 ° C. Postoperatively, the patients were transferred to postoperative recovery and then to abdominal surgery high dependency unit.

Before surgery, immediately after surgery and then on postoperative days 1 and 2, the concentrations of biomarkers S-100, NSE, GFAP, MMP-9, apolipo-E4, UCH-L1, tau were measured. Blood samples were collected without additives. Serum was separated after centrifugation (1500 g for 10 min) and aliquots were stored at –80 °C until analysis. NSE and protein S-100 were measured by automated electrochemiluminescence assay (reagents and analyzer: Roche Diagnostics, Mannheim, Germany) with a detection limit of 0.05 μg/L and 0.005 μg/L, respectively. For the measurement of GFAP and Tau sandwich ELISA immunoassays were used (BioVendor, Brno, Czech Republic); the limit of detection was 0.05 μg/L for GFAP and 1.0 ng/L for Tau. The same principle of ELISA immunoassay was used for UCH-L1, Apo-E4 and MMP-9 (Thermo Fisher Scientific, Frederick, MD, USA), the limit of detection was 0.8 μg/L, 0.4 μg/L and 0.5 μg/L, respectively. All ELISA protocols were performed according to the manufacturer"s instructions. Samples were analysed in one batch.

Cognitive clinical status was assessed using Mini Mental State Examination (MMSE) before the surgery and on the second postoperative day.

Statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). A One-Way Analysis of Variance (ANOVA) for repeated samples was specifically employed to determine the variations in levels of biomarkers across the four time-points.

3. Results

Laboratory samples from 27 patients were collected at four different time-points.

Average age was 65.1 (± 12.7) years, 16 male and 11 females were included. Duration of surgery was 161 ± 72 min and duration of hospitalisation was 10.9 ± 4.8 days. Comorbidities were graded according to American Society of Anaesthesiologist (ASA) status. 9 patients were ASA 2, 17 ASA 3 and 1 ASA 4.

The analysis used linear regression to evaluate the relationship between the duration of surgery (independent variable) and various biomarkers measured at different time points (dependent variables). No significant correlation was fund.

Levels of biomarkers from preoperative value (sample 1), immediately after surgical procedure (sample 2) and two subsequent consecutive days (samples 3 and 4) are shown in Figures 1 – 3.

The results and the analysis of variance have shown significant difference in NSE concentration ($p = 0.08$), S-100 ($p = 0.001$) and MMP-9 ($p = 0.004$).

MMSE scores before surgery was 28.0 ±1 .93 and after surgery 28.0 ± 2.04. There was no difference between the results in MMSE before and after surgery (Paired t-test t-statistic: 0.51, p-value: 0.615). There is no significant relationship between the duration of surgery and MMSE scores post-operatively (Pearson correlation coefficient, $r = –0.16$, $p = 0.414$).

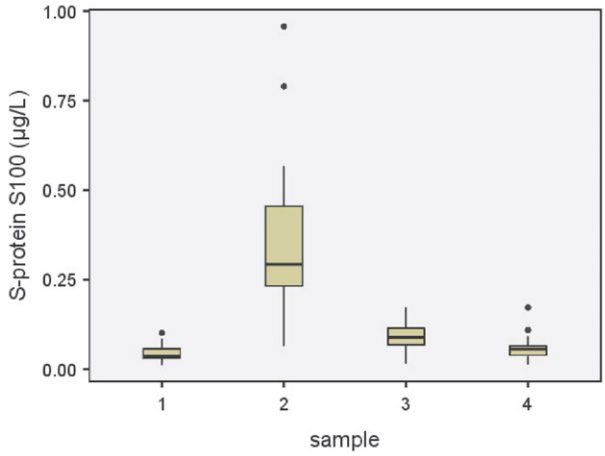

Figure 1. Box plot representing median and 25–75 percentiles of NSE in serum at four time-points: Before surgical procedure, immediately after surgical procedure and next two consecutive postoperative days (median and quartiles and minimum and maximum; points represent outliers).

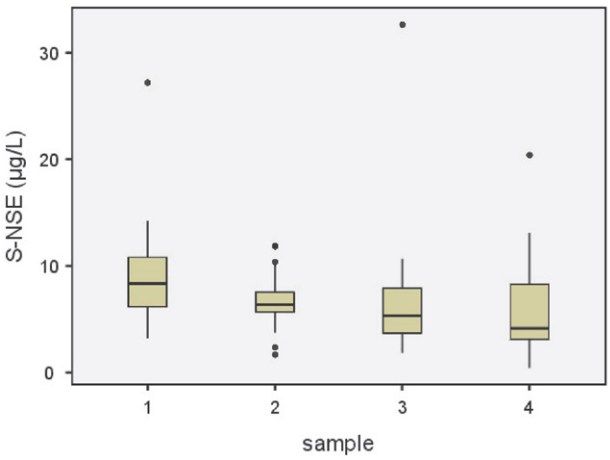

Figure 2. Box plot representing median and 25–75 percentiles of S-100 in serum at four time-points: Before surgical procedure, immediately after surgical procedure and next two consecutive postoperative days (median and quartiles and minimum and maximum; points represent outliers).

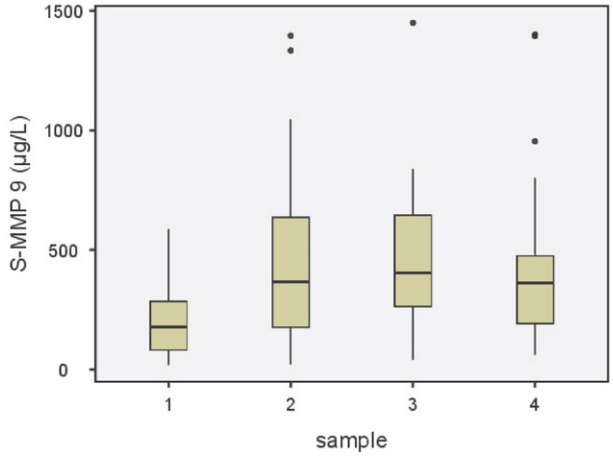

Figure 3. Box plot representing median and 25–75 percentiles of MMP-9 in serum at four time-points: Before surgical procedure, immediately after surgical procedure and next two consecutive postoperative days (median and quartiles and minimum and maximum; points represent outliers).

3. 1. Discussion

Based on our results, proteins MMP-9 and S-100 show the concentration profile, which is in accordance with intraoperative cerebral injury. Before the procedure, the concentrations of biomarkers were low. The highest level was measured immediately after the procedure and a rapid decrease of S-100 together with gradual decrease of MMP-9 was measured in the following days. However, S-100 plasma levels were within the normal reference range. This indicates that even in balanced anesthesia and without clinically apparent consequences there might be an intraoperative cerebral injury.

S-100 proteins, particularly S-100B, are primarily found in astrocytes and are released into the extracellular space after neural injury. The release mechanism is believed to involve a disruption of the blood-brain barrier or cellular damage. Once released, S-100B can act both in a neurotrophic and a neurotoxic manner, depending on its concentration. Low concentrations generally have neurotrophic effects that promote neuronal survival and neurite extension. On the contrary, higher concentrations are often associated with neuroinflammation and apoptosis.[19] The pathophysiology behind the release of the S-100 protein is complex and involves multiple pathways that include calcium signaling, inflammation, and oxidative stress. Elevated levels of S100 proteins are often considered to be a marker for various pathological conditions, including traumatic brain injury, neurodegenerative dis-

eases, and conditions involving cerebral ischemia.[20] Protein S-100 was also studied as a marker of perioperative cerebral injury in cardiac and non-cardiac procedures.[21]

MMP-9 is an enzyme that degrades components of the extracellular matrix, specifically glycocalyx. It plays a role in tissue remodeling, inflammation, and angiogenesis. Clinically, elevated levels of MMP-9 have been associated with various pathological conditions including cancer metastasis, cardiovascular diseases, and neurological conditions such as stroke and multiple sclerosis. In the context of neurology, MMP-9 has gained attention for its role in disrupting the blood-brain barrier, which can be critical in conditions such as stroke and traumatic brain injury. The expression of MMP-9 around leaky blood vessels is increased and is related to degradation of glycocalyx. Elevated MMP-9 levels have been linked to worse clinical outcomes, such as larger infarct sizes in ischemic stroke.[22] Perioperatively surgical stress increases release of MMP-9 and its enzymatic activity.[23] Careful choice of anesthesia technique can have a protective effect on glycocalyx. Intravenous anesthesia with propofol, due to similarity of propofol molecule with endogenous vitamin E reduces glycocalyx shedding. Epidural anesthesia decreases sympathetic activity and lowers the patients' plasma level of superoxide dismutase and oxidative stress.[24] Appropriate intraoperative fluid management can also have protective effect.[25] Cognitive dysfunction after carotid surgery corelates to higher pre- and postoperative plasma levels of MMP-9.[26]

Serum NSE level is a diagnostic and prognostic marker that is correlated with the extent of brain damage. In adult perioperative patients with no known central nervous system (CNS) lesions, an increase of NSE concentration in serum can be explained by subclinical damage to brain cells that undergo reversible changes like diffuse microembolism and increased blood–brain barrier permeability.[27] In cerebrospinal fluid, the NSE concentration was increased after aortic aneurysm repair surgery regardless of the presence or absence of neurological symptoms. [21] Changes in Alzheimer's disease markers and astroglial cell integrity, as well as evidence of opening of the blood-brain barrier were also found in the cerebro- spinal fluid (CSF) of patients after hip arthroplasty.[28] In these patients, significant amounts of pro- and anti-inflammatory markers are detectable in the plasma and CSF of older adults after knee and hip replacement surgery.[29,30] Following our results, there were no increases in NSE after surgical procedure. This might be due to the intraoperative fluid infusion, which could lower the level of NSE. The perioperative profile without significant rise after the procedure might also show the benefits of neuroprotective anesthesia. NSE values were also within the normal reference range.

Major risk factor for cognitive impairment include apolipo-E4 genotype. Circulating apolipo-E4 inhibits enzyme activity of endothelial nitric oxide synthase. Loss of endothelial nitric oxide function activates microglia and creates pro-inflammatory environment in the brain.[31] Tau is a microtubule-associated protein that stabilizes the axonal microtubules in the brain and spinal cord. Phosphorylation of tau is associated with neural death, as observed in Alzheimer disease.[21,31] Tau level raises postoperatively. 6 h after surgery it reaches its peak and the fourth postoperative day it returns to baseline. Postoperative cognitive disorders after cardiac and aortic surgery corelate to higher serum levels of tau.[32] Biomarkers UCH-L1 and GFAP may help detect brain injury, assess its severity, and improve outcome prediction.[33] UCH-L1 is a highly specific neuronal protein, only small amounts arise from other tissues, which makes it a specific biomarker of CNS insults. It was connected to degenerative CNS disease and to subarachnoid hemorrhage, but there are no studies of the predictive value of UCH-L1 in the perioperative period.[21] Levels of GFAP is, like S-100B, astroglial cell injury marker and is increased after major surgery.[34]

Although we did not observe statistically significant differences in levels of proteins UCH-L1, apolipo-E4, tau, GFAP in perioperative period, we observed some interesting correlations. Two patients with preoperatively high levels of UCH-L1 had also postoperative rise of NSE and S-100. Due to limited number of patients, the statistic was not preformed. High preoperative levels of NSE in one patient were lower in postoperative period. There was also no correlation with high levels of other biomarkers.

Perioperative neurocognitive decline, observed primarily in the elderly, is related to a systemic inflammatory response, following the surgical procedure.[35] It is also related to the depth of anesthesia, the accompanying cerebrovascular disorders, and the age of the patients. In patients older than 60 years, the incidence of perioperative neurocognitive decline 3 months after surgery was found to be 12 %.[36] Neuroprotective anaesthesia might prevent perioperative neurocognitive decline. Compared to other studies, our patients were a homogeneous group in terms of type of surgery and anesthesia. During anesthesia, we have used the technique with maximum possible cerebral protection. Dexmedetomidine, a highly selective α_2 adrenoceptor agonist, is used perioperatively to reduce pain intensity, analgesic consumption, and nausea.[37] It also preserves cognitive function in elderly patients, probably by decreasing the systemic inflammatory response and therefore acts neuroprotectively and may also prevent postoperative delirium. [37,38] To eliminate the influence of drugs on cognitive function, we avoided those with a known effect of worsening cognitive function, such as midazolam or opioids. Instead, we used epidural analgesia and dexmedetomidine, which reduce perioperative opioid consumption.[39]

Especially in elderly people, mortality and morbidity in general, but also cognitive decline, are related to too deep anaesthesia. Monitors that assess the degree of cortical suppression (e.g. BIS) facilitate anaesthetic titration and have been shown to reduce anaesthetic exposure and

decrease the risk of postoperative cognitive dysfunction.[40] In our study, intraoperative propofol consumption was reduced by dexmedetomidine.[41] Intraoperatively, our patients were also fluid optimised according to hemodynamic values. Such a strategy prevents oedema, inflammatory response, and cognitive decline. Despite the postoperative increase in some neuroinflammatory biomarkers, no clinically evident cognitive consequences were observed and change in MMSE.

Unlike liver transplantation and cardiopulmonary bypass operation, colorectal surgery is not related to ischemic-reperfusion injury, causing a severe systemic inflammatory response and an increase in brain biomarkers. On the other hand, orthopaedic surgery is similar in duration and extent of operation, but increased brain biomarkers were also observed.[42–44] In our study, brain biomarkers did not increase significantly.

In the present study, all patients had the same type of operation (colorectal resection), with similar duration and extent of tissue damage, probably related to the similar systemic inflammatory response. The duration of the surgical procedure and the extent of tissue damage are documented to correlate with the systemic inflammatory response.[45–48]

4. Conclusions

In conclusion, the study highlights the differential expression of MMP-9 and S-100 proteins as biomarkers of cerebral injury in the context of balanced anesthesia during major abdominal surgery. These proteins may serve as valuable indicators for intraoperative cerebral injury, potentially leading to the development of more precise diagnostic and monitoring tools.

Our study also showed, that the use of known neuroprotective anesthesia reduced neuroinflammation and kept cerebral injury biomarkers S-100 and NSE within normal values.

The implications of the study extend to potentially improving patient outcomes by allowing earlier detection and intervention for perioperative neurocognitive disorders. Future research should focus on validating these biomarkers in larger and diverse cohorts of patients and exploring the mechanistic pathways that underlie biomarker release and neuroinflammation in the perioperative setting.

Trial registration

ClinicalTrials.gov, NCT02293473, https://clinicaltrials.gov/

Declaration of interest

None declared.

5. References

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Povzetek

Perioperativni nevrokognitivni upad predstavlja za bolnike tveganje za resne zaplete, vključno z demenco in celo smrtjo. Namen naše študije je bil opazovati spremembe v koncentracijah biomarkerjev nevroinflammacije, ob uporabi optimizirane anestezije in brez kliničnih znakov perioperativnega neurokognitivnega upada. V našo observacijsko študijo smo vključili kirurške bolnike z visokim tveganjem za zaplete, ki so prestali obsežne resekcije debelega črevesa. Uporabili smo uravnoteženo anestezijo z namenom najboljše zaščite možganov. Med operacijo in po njej smo v serumskih vzorcih z uporabo imunokemičnih metod merili koncentracijo NSE, proteina S-100, matriksne metaloproteinaze-9 (MMP-9) in drugih označevalcev poškodbe možganov. Koncentracijska profila proteina MMP-9 in S-100 sta bila skladna z možnostjo medoperativne poškodbe možganov. Kljub porastu so vrednosti S-100 in NSE v plazmi ostale znotraj normalnega območja. Koncentracija NSE je celo upadla, verjetno zaradi intraoperativne infuzije. Naša študija je pokazala, da uporaba nevroprotektivne anestezije lahko zmanjša stopnjo vnetja. Študija poudarja izražanje proteinov MMP-9 in S-100 kot možnih označevalcev možganske poškodbe v kontekstu uravnotežene anestezije med večjimi trebušnimi operacijami.