Published in final edited form as:
Anesthesiology. 2011 October ; 115(4): 727–732. doi:10.1097/ALN.0b013e31822e9306.

Human Alzheimer and inflammation biomarkers after anesthesia and surgery

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Abstract

Background—The prevalence of post-operative cognitive disturbance, coupled with growing *in vitro*, cell and animal evidence suggesting anesthetic effects on neurodegeneration, calls for further study of the interaction between surgical care and Alzheimer neuropathology. Here, we study human cerebral spinal fluid (CSF) biomarkers perioperatively.

Methods—Eleven patients undergoing idiopathic nasal CSF leak correction joined this Institutional Review Board approved study. Lumbar subarachnoid catheters were placed prior to the procedure. Anesthesia was total intravenous anesthesia (propofol/remifentanil) or inhalational (sevoflurane), depending on provider choice. CSF samples were taken after catheter placement (base), at procedure end (0h), and then at 6, 24 and 48h. CSF was analyzed using xMAP Luminex immunoassay (Luminex, Austin, TX).

Results—Patients: 53±6 yrs old; 8 women; 4 received intravenous anesthesia, 6 sevoflurane, 1 mixed. Procedures lasted 6.4 ± 2h. Mean CSF amyloid-$\beta_{1\text{-}42}$ remained unchanged, but total-tau and phosphorylated-tau181P increased progressively until at least 48h. Total-tau, phosphorylated-tau or amyloid-$\beta_{1\text{-}42}$ levels were not different between anesthetic groups. CSF interleukin-10, S100B and tumor necrosis factor alpha were increased similarly in both anesthetic groups at 24h, but interleukin-6 was increased more in the inhalational group.

Conclusion—These data indicate a robust neuroinflammatory response, including not only the usual markers (interleukin-6, tumor necrosis factor α, interleukin-10), but also S100B and tau, markers of injury. The total-tau/amyloid-$\beta_{1\text{-}42}$ ratio increased in a pattern consistent with Alzheimer disease, largely due to an increase in total-tau rather than a decline in amyloid-$\beta_{1\text{-}42}$. The differences in CSF interleukin-6 levels, suggest that anesthetic management may make a difference in neuroinflammatory response.

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Introduction

The possibility that anesthesia and surgery produces durable cognitive losses has gained attention over the last decades, but evidence remains ambiguous and controversial. Our patients and their families have long suspected that something about surgery accelerates age-related cognitive decline, and are beginning to demand specific approaches and drugs in their preoperative visits. Further, the possibility that anesthesia may specifically target Alzheimer disease pathways,[1] has stimulated considerable research at all levels.[2] For example, anesthesia alone can accelerate amyloid beta production[3;4] and aggregation,[1;5] as well as tau phosphorylation and aggregation.[6] Surgery may have an independent effect on these pathways.[7] Much of this flows from studies in cell culture and animals. Human data are essential, but the decades-long refractory period, when Alzheimer's pathology is developing in the absence of detectable cognitive symptoms, has made the research difficult to conduct when relying on cognitive tests. In fact, a recent state-of-the-science conference on Alzheimer treatment[8] has concluded that, despite enormous numbers of studies, there exists no definitive evidence for the ability of any pharmaceutical, environmental or life style factor to modulate the trajectory of the most common form of Alzheimer's disease (late-onset type). This is due not only to the long time periods involved, but also to reliance on ambiguous, and poorly defined outcome measures. Thus, validated biomarker and imaging outcomes are strongly needed to make any progress on the interaction between the surgical care and Alzheimer neuropathology and dementia.

Currently, the only validated biomarker to aid a diagnosis of Alzheimer's disease is the cerebral spinal fluid (CSF) total tau (t-tau) to amyloid-beta$_{1-42}$ (Aβ_{1-42}) ratio. In Alzheimer's disease, the ttau to Aβ_{1-42} ratio is greater than about 0.5.[9] The consortium of Alzheimer's Disease Neuroimaging Initiative (ADNI) centers currently does not measure the other major form of amyloid beta (Aβ_{1-40}), but has found that increased levels of phosphorylated tau181P (p-tau$_{181p}$) is useful as a sensitive predictor of cognitive decline in initially cognitively normal patients.[10] There is intense interest in the use of imaging modalities, but these are still considered experimental. Blood tests are desirable, but are insufficiently validated at present. Obtaining CSF in surgical patients is challenging. First, many patients refuse an additional invasive procedure in the perioperative period, unless it is part of their care. Second, CSF levels of these biomarkers may undergo diurnal variation.[11;12] Studies suggest that amyloid-β levels simply reflect synaptic activity[13], and therefore level of arousal. Technical and biological variation in CSF biomarker measurements can be large,[14;15] something to which the ADNI consortium has devoted considerable effort. Although there are few studies of the effect of an acute intervention on the CSF levels of Alzheimer disease biomarkers, a recent report showed that cardiac surgery patients showed an increase in injury biomarkers (S100B and tau) in their CSF, and decreases in Aβ six months post-operatively[16]. This pattern is characteristic of Alzheimer patients. However, in the first hours or days after an intervention, it is not clear in which direction Aβ peptides are likely to change. For example, Aβ production via beta-secretase activation [4] might *increase* CSF Aβ and add to brain amyloid burden. On the other hand, accelerated aggregation would *decrease* free Aβ peptides. Thus, to begin address this question, we collected CSF from patients undergoing routine surgical procedures.

Materials and Methods

After 18 months of recruitment for these somewhat uncommon procedures, the single surgeon conducting them elected to discontinue the approach. Thus, eleven otherwise healthy patients scheduled for endoscopic nasal surgery to correct idiopathic CSF leaks were enrolled in this Institutional Review Board (University of Pennsylvania, Philadelphia, PA) approved study with written/informed consent. There was no evidence of cognitive

impairment and infection, and no patients were taking central nervous system (CNS)-active medications. These procedures included, as part of their normal care, lumbar drains placed at the time of surgery by the anesthesiologist, in order to a) infuse fluorescein to facilitate leak identification, and b) to maintain low CSF pressures to permit healing of the closure. The drains are typically left in place for 48 to 72h post-operatively, and drained CSF is typically discarded. Exclusion criteria included; age less than 40, known dementias, epilepsy, or any CNS/intracranial process that might influence the CSF results.

Lumbar subarachnoid catheters were placed immediately prior to administration of the anesthetic and the surgical procedure. Anesthetic management depended entirely on provider choice and was therefore not randomized. However, the providers for these cases fall neatly into two camps, those that always use inhalational agents for maintenance, mostly sevoflurane, and those that always use total intravenous anesthesia (TIVA), using a combination of propofol and remifentanil. All patients were intubated with the aid of vecuronium, and mechanically ventilated. The first, or baseline, CSF sample of 1-2 mls was taken at the time of lumbar drain placement. Another CSF sample was taken at the end of the procedure (0 time), and then additional samples at 6, 24 and 48h later, or until the catheters were removed. All patients had at least 4 samples (baseline, 0, 6 and 24h) and six had an additional sample at 48h. Samples were collected roughly at the same time of day (± 3h). All samples were aliquoted into 1.5 ml plastic microcentrifuge tubes and immediately frozen at -80°C for subsequent batch analysis.

Alzheimer Biomarkers

Because of well-known inter-laboratory variability, and the effort undertaken to standardize the ADNI laboratories, we submitted aliquots of all our samples to the University of Pennsylvania ADNI biomarker laboratory.[17] Briefly, $A\beta_{1\text{-}42}$, t-tau, and p-tau_{181p} were measured in each of the aliquots using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use–only reagents) immunoassay kit–based reagents. These kits included well-characterized capture monoclonal antibodies specific for $A\beta_{1\text{-}42}$ (4D7A3), t-tau (AT120), and p-tau_{181p} (AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7, 3D6). Calibration curves were produced for each biomarker using aqueous buffered solutions that contained the combination of three biomarkers at concentrations ranging from 56 to 1,948pg/ml for recombinant tau, 27 to 1,574pg/ml for synthetic $A\beta_{1\text{-}42}$ peptide, and 8 to 230pg/ml for a synthetic p-tau peptide phosphorylated at the threonine 181 position.

Inflammatory Biomarkers

Other aliquots were analyzed for inflammatory biomarkers, also with Luminex xMAP technology[18] (Luminex Corp) in the Human Immunology Core of the University of Pennsylvania. Commercial MILLIPLEX MAP kits (Millipore, Billerica, MA) were used in this study to quantify cytokines and neurodegenerative biomarkers in CSF samples, except for S100B, which was quantified with an enzyme-linked immunosorbent assay (ELISA) kit (Abnova, Taipei City, Taiwan, catalog# KA0037). Interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α, and vascular endothelial growth factor were simultaneously quantified using Human Cytokines/Chemokines Panel - 5 Plex kit (Millipore, catalog# MPXHCYTO-60K-05). Luminex bead assays were performed according to the manufacturer's instructions. After thawing, CSF samples were added in duplicate to a 96-well filter-bottom plate and incubated overnight at 4°C with antibody-coated beads which were internally coded with fluorescent dyes. After washing, biotinylated detection antibody was added and 1h later, the streptavidin-phycoerythrin conjugate, was added. After washing again, sheath fluid was added and the plate was read on the

BioPlex200 instrument (Bio-Rad, Hercules, CA). Standard curves with appropriate background media were run for every plate. Calibration curves were used to convert the median fluorescent intensity readings for each sample to concentrations (pg/ml) using a five-parameter logistic model.

Statistical Analysis—A repeated measures 1-way analysis of variance (ANOVA) , with the Bonferroni post-hoc test, was used to test statistical differences in the samples out to 24h, for which the n=11 at each time point. The 48h time point (n=6) is shown in the figures for illustrative purposes. For the stratification by anesthetic technique, a repeated measures 2-way ANOVA design, with the Bonferroni post-hoc test, was used with GraphPad Prism 5.0 software (La Jolla, CA).

Results

Patients were 53±6 years old, 8 were women and all were American Society of Anesthesiologists status I or II. Six patients received TIVA, four received sevoflurane for maintenance, and for one it was mixed. The procedures lasted 6.4 ± 2h, much of the time being required for stereotactic imaging set-up and the microdissection through the endoscope. Patients were euthermic throughout, and none experienced unusual changes in physiology. Procedures were without complications from either the surgery or the anesthesia/lumbar drain. Mean CSF $A\beta_{1\text{-}42}$ levels fluctuated by less than 10% in either direction, and were statistically unchanged over the 24h post-operative period (Fig. 1A). Total tau, on the other hand, was significantly increased after 6h, more than 200% after 24h (Fig. 1B). The data suggest it may still be increasing even at 48h post-operatively. The ratio of t-tau to $A\beta_{1\text{-}42}$ exceeded 0.5 at 48h (Fig. 1C), considerably higher than the 0.39 level used as a cutoff for mild cognitive impairment in the ADNI patient set.[17] Although less dramatic, CSF levels of a pathologic p-tau_{181p}, were also elevated (~23%) post-operatively (Fig. 1D). Another “injury” biomarker, S100B, followed a similar course in the CSF as t-tau (Fig. 2). The inflammatory biomarkers, IL-10, IL-6 and tumor necrosis factor α were also significantly increased over time after surgery (Fig. 3A-C), while no consistent change was observed in IL-1β or vascular endothelial growth factor (data not shown). Although the numbers of patients were small, we were able to detect a significant difference in IL-6 levels between the anesthetic management approaches. Maintenance with sevoflurane was associated with a higher post-operative CSF IL-6 concentration as compared to TIVA (Fig. 4). There were too few men to make a gender comparison, and too few patients overall to stratify the results according to procedure duration.

Discussion

Despite the small numbers of patients enrolled in this biomarker study, several observations are of interest. First, the standard, diagnostic measure of Alzheimer's disease, $A\beta_{1\text{-}42}$ remained unchanged throughout the perioperative period. In Alzheimer's disease, this biomarker is lowered to 144 ± 41 pg/ml in the CSF,[17] presumably due to sequestration into senile plaque, although there might also be less release into the extracellular space because of the synaptic destruction characteristic of this neurodegenerative process.[19] Even mild cognitively impaired patients have CSF $A\beta_{1\text{-}42}$ levels that are significantly lower than observed here at any time point (164 ± 55 pg/ml). Few studies on the effect of an acute intervention have been conducted however, so it is not clear whether any acute changes in CSF $A\beta_{1\text{-}42}$ are to be expected even if the intervention were known to enhance Alzheimer's neurodegeneration.

On the other hand, the dramatic and progressive increase in CSF t-tau does suggest that an acute CNS injury of some sort has occurred. Tau is a microtubule associated protein that

normally has an intracellular location. On hyperphosphorylation, it dissociates from microtubules, and can then aggregate to form paired helical filaments and when in excess, neurofibrillary tangles, a hallmark intracellular lesion of Alzheimer's disease. The appearance of tau in CSF is likely to reflect cellular damage and release rather than the more complex $A\beta_{1-42}$ process, which involves proteolysis, release, oligomerization and extracellular plaque formation. This is consistent with the elevation in CSF S100B. Even though considered non-specific, there exists consensus that S100B elevation reflects CNS injury, most likely due to release from astrocytes, Schwann cells and other CNS cell types. While some may speculate that the anesthetic drug itself is responsible for the stress or cytotoxicity underlying the biomarkers, the similar changes observed with very different anesthetic approaches renders this somewhat less likely. It is perhaps more likely due to the surgery-induced inflammatory cascade, for which we provide ample biochemical evidence, as has been observed in brain tissue from wild type mice undergoing hepatectomy.[7] We cannot rule out, however, that the changes in tau and S100B are due to local tissue damage caused by the surgeon in the vicinity of the CSF leak repair. This seems unlikely since tau and S100B are considered to have a CNS origin, and have a different time course after tissue injury than observed here.[20]

The ratio of t-tau to $A\beta_{1-42}$ after 24h post-operatively approximates that seen in patients with diagnosed mild cognitive impairment.[9] It is important to point out, however, that in the ADNI study, the progressive increase in this ratio is driven primarily by a larger decrease in $A\beta_{1-42}$ and a smaller increase in t-tau. Since the increase in this ratio in our patients is driven almost entirely by an increase in t-tau, the significance with respect to Alzheimer neuropathology remains unclear.

Allthough smaller in magnitude than t-tau, the repeated measures ANOVA indicated a significant time effect in CSF p-tau_{181p} perioperatively (Fig. 1D), with levels elevated over 20% at 6 and 24 h as compared to immediate post-operative samples. Tau phosphorylation is antecedent to microtubule detachment and destabilization, in addition to neurofibrillary tangle formation, a hallmark lesion of Alzheimer's disease. Increases in CSF p-tau_{181p} have been found to be the most sensitive predictor of cognitive decline in otherwise cognitively normal patients.[10] Thus, CSF p-tau_{181p} should be considered as a potentially useful biomarker for postoperative cognitive decline in future studies, and perhaps risk stratification. Whether it can be considered a predictor of Alzheimer's dementia in these patients is unclear.

Our data clearly indicate that anesthesia and surgery initiate an acute pro-inflammatory event in the CNS, consistent with recent studies in both humans[21] and animals.[22] The pro-inflammatory cytokines IL-6 and tumor necrosis factor α were all elevated in the 24-48 h following surgery, and the “anti-inflammatory” IL-10 became modestly elevated. Surgical initiation of inflammatory cascades is well-known in the periphery,[23] but has been less well documented in the CNS, where it would be considered “neuroinflammation”. Enhanced neuroinflammation is hypothesized to worsen Alzheimer neuropathology, and thus our results may indicate one mechanism by which the perioperative period might modulate ongoing neurodegeneration. Most interestingly, we detected a significant difference in IL-6 levels between anesthetic management approaches. Maintenance with the inhalational anesthetic sevoflurane was associated with significantly higher CSF IL-6 levels than maintenance with TIVA (propofol and reminfentanil). Although this finding is consistent with the repeated observation of inhaled anesthetic-induced neurotoxicity (usually isoflurane), it should be emphasized that few side-by-side comparisons with TIVA have been conducted, so it cannot yet be concluded that TIVA is less neurotoxic or neuroinflammatory than inhalational general anesthesia. Although the significance of an isolated CNS IL-6 change is not clear, the difference in IL-6 levels between these two

approaches is not small, and may indicate either a more pro-inflammatory effect of sevoflurane or a more cytotoxic effect that secondarily triggers IL-6 release.

Summary

This biomarker study indicates that anesthesia and surgery evoke a robust neuroinflammatory response, and an injury response marked by large increases in t-tau and S100B. Limited evidence suggests that anesthetic management may modulate this inflammatory response. The lack of effect of anesthesia and surgery on $A\beta_{1\text{-}42}$ suggests the lack of a specific interaction with amyloidopathy pathways, although a small effect on CSF p-tau_{181p} suggest a potential interaction with tauopathy pathways. The relevance of these observations to long term consequences must be tempered by the fact that few biomarker studies after an acute intervention have been performed, and the evolution of biomarker changes remains unclear.

Acknowledgments

Support was provided solely from Institutional and/or departmental sources.

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Summary Statement

Human cerebral spinal fluid biomarkers for Alzheimer's disease and inflammation are altered within 48h of endoscopic nasal surgery towards an injury and neuroinflammatory pattern. Differences between inhalational and total intravenous anesthetic approaches were detected.

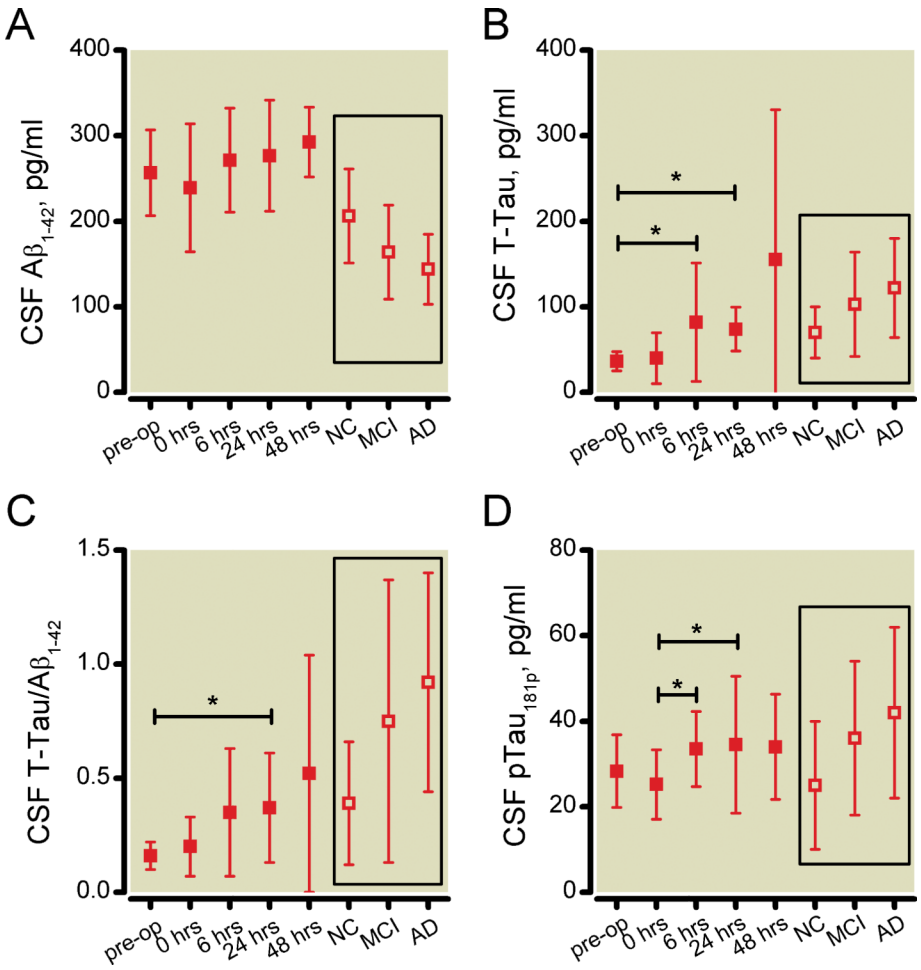

Figure 1. Changes in Alzheimer biomarkers in the cerebral spinal fluid perioperatively

(A-D), the shaded boxes with open circle data points contain data (mean ± SD) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort of patients[17] for comparison purposes only. NC, normal cognition (n=114); MCI, mild cognitive impairment (n=196); AD, Alzheimer disease (n=100). The solid black circles are data from this study. (A) No change is seen in amyloid-beta$_{1-42}$ (Aβ_{1-42}) cerebral spinal fluid (CSF) levels (F=2.39, P=0.09) over time but (B) a significant increase in total tau (T-tau) is detected (F=10.35, P= 0.0006), producing (C) an increase in the T-tau/Aβ_{1-42} ratio (F=2.96, P=0.048). (D) Phosphorylated tau181P (p-tau$_{181p}$) shows a significant time effect (F= 4.71, P= 0.008). Points are mean ± SD, n=11 for all time points except 48h, where the n=6 (see Materials and Methods, Statistical Analysis section), *P<0.05 using repeated measures 1-way ANOVA and the Bonferroni post-hoc test.

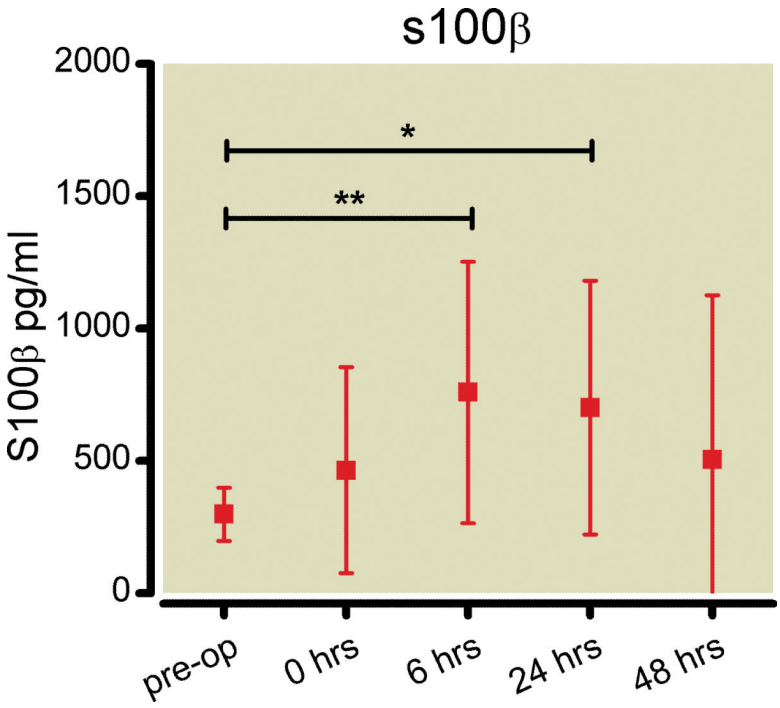

Figure 2. Changes in cerebral spinal fluid levels of S100B perioperatively

Significant elevations in this injury biomarker, S100B, are seen at 6 (**P<0.01) and 24 h (*P<0.05) postoperatively in the cerebral spinal fluid (CSF) using repeated measures 1-way ANOVA with the Bonferroni post-hoc test. There is also an overall significant effect over time (repeated measures 1-way ANOVA, F= 6.62, P=0.0015). Points are mean ± SD; pre-op to 24h (n=11), 48h (n=6) (see Materials and Methods, Statistical Analysis section).

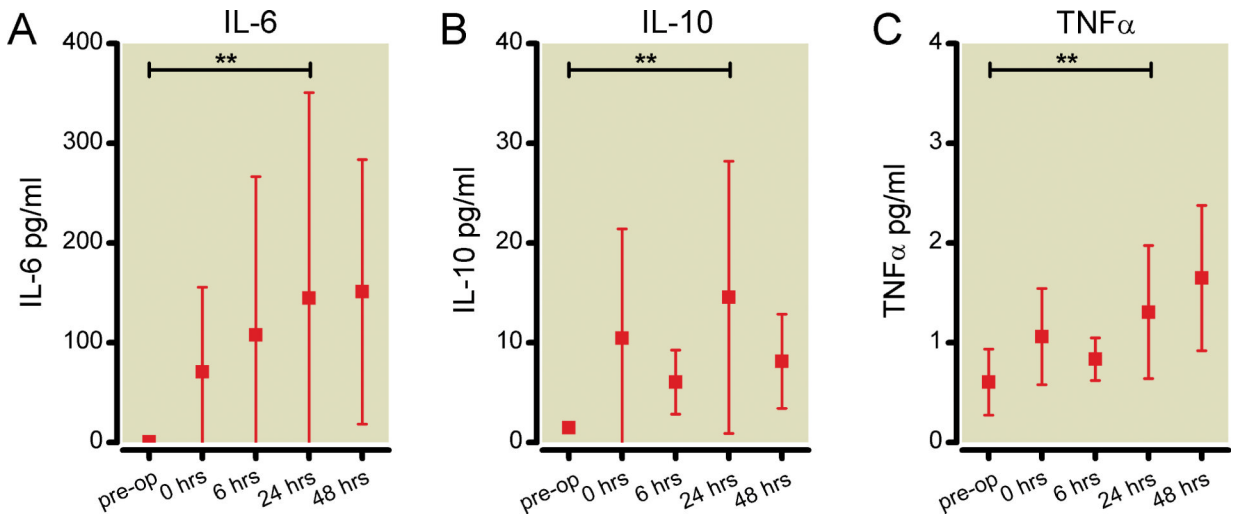

Figure 3. Cerebral spinal fluid inflammatory biomarkers in the perioperative period

(A) Significant elevations are detected in interleukin-6 (IL-6) (F=4.59, P=0.01), (B) interleukin-10 (IL-10) (F=4.69, P=0.008) and (C) tumor necrosis factor alpha (TNF-α) (F4.66, P=0.009) post-operatively in the cerebral spinal fluid (CSF). In each case, the 24h point was significantly increased using repeated measures 1-way ANOVA with the Bonferroni post-hoc test (**P<0.01). Points are mean ± SD; pre-op to 24h (n=11), 48h (n=6) (see Materials and Methods, Statistical Analysis section).

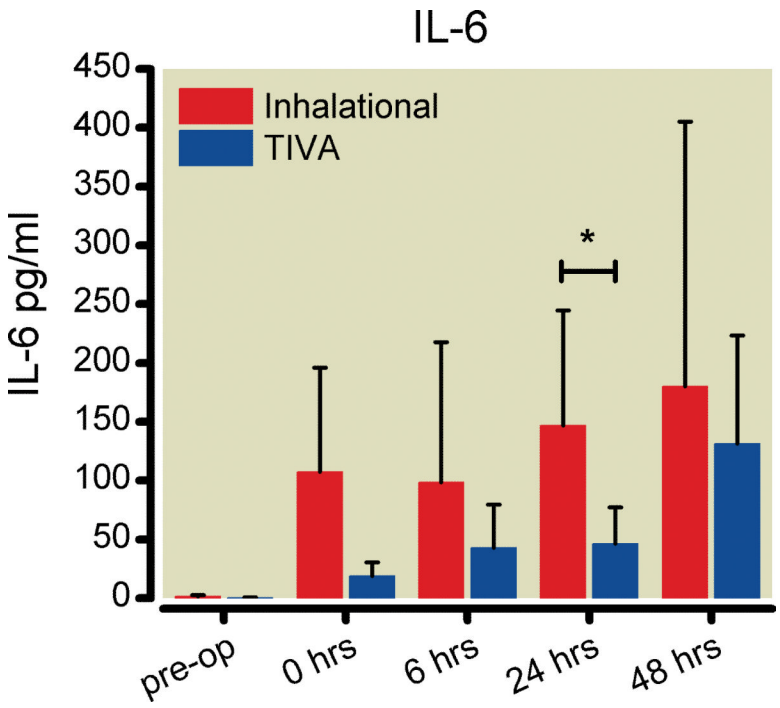

Figure 4. Cerebral spinal fluid IL-6 response stratified by anesthetic technique

Interleukin-6 (IL-6) levels in the cerebral spinal fluid (CSF) were found to have a significant treatment effect (by repeated measures 1-way ANOVA, F=5.50, P=0.031) in the post-operative period when sevoflurane (n=4) was used instead of total intravenous anesthesia (TIVA) (propofol and remifentanil) (n=6). Due to the small n values and variation, no specific time point was significantly different by Bonferroni post-hoc test.