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[SNACC-1] Inhibition of RhoA Activity with TAT-C3 Attenuates Propofol-mediated Neurotoxicity

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Background: Propofol (PPF) exposure to developing neurons during synaptogenesis results in neurodegeneration; the resulting cognitive dysfunction in adulthood has bene attributed to apoptosis. However, recent data indicate that apoptosis per se might not be the primary mechanism that leads to cognitive dysfunction. Anesthetic induced disruption of neuronal cytoskeleton leads to loss of neuritis, dendrites and synapses, thereby disrupting development of neuronal networks. PPF induced activation of RhoA plays a central role in neurite loss. Inhibition of RhoA might prevent PPF toxicity. To determine whether RhoA inhibition prevents neurite loss and prevents the adverse effects of PPF on the development of neuronal networks in the hippocampus, we investigated the effect of TAT-C3, a RhoA inhibitor, on neurite loss in cultured rodent neurons and in mice in vivo. Similar studies were undertaken in human neurons in vitro to determine whether RhoA is of relevance to PPF toxicity in human tissue.

Methods: Primary fetal human neurons (Advanced Bioscience Resources, Alameda, CA) and postnatal day 5-7 (PND5-7) mice were exposed to PPF (3 μM) or DMSO for 6 hours, with pre-treatment of TAT conjugated C3 (TAT-C3) (50 ug/mL, 2 h), a highly specific pharmacologic inhibitor of RhoA or TAT control. RhoA activation was evaluated by staining for RhoA-GTP (active form). Dendritic spine changes were evaluated with the neuronal spine marker, drebrin. Changes in synapses in PND5-7 mouse hippocampi were assessed by electron microscopy. Histological sections of the entire hippocampus were stained for synaptoporin to quantify the area and volume of suprapyramidal and infrapyramidal mossy fibers from the dentate granule neurons to the CA3 pyramidal neurons (SPM and IPM, respectively) in vivo.

Results: Exposure of human neurons in vitro to PPF increased active RhoA, decreased drebrin staining, and decreased dendritic arborization. These adverse effects of PPF were mitigated by TAT-C3. These are the first data in human neurons to demonstrate PPF neurotoxicity. In PND7 rodent pups exposed to PPF, a reduction in SPM was apparent. By 1 week after exposure, the SPM fibers were restored. By contrast, there was a significant reduction in IPM volume that was apparent even 4 weeks post exposure.

Conclusions: Our previous results, which demonstrated that PPF induced toxicity was prevented by RhoA inhibition in rodent neurons, were recapitulated in human neurons. These data indicate that RhoA may also play an important role in anesthetic neurotoxicity in human tissue. In addition, our results demonstrate that PPF causes a dramatic alteration in neuronal networks in vivo. A single exposure at PND7 led to persistent alteration of the mossy fibers of hippocampus four weeks post exposure (at PND35). This alteration in the architecture of the hippocampus may contribute to cognitive dysfunction in adulthood.

[SNACC-2] Effect of Early Repeated Anesthetic Exposure on Long-term Cognition

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Background: Early anesthetic exposure in humans and rodents leads to long-term cognitive effects. In rodents, longer exposures result in worse outcomes.[1] Studies have also demonstrated that multiple anesthetic exposures may be more harmful than a single exposure.[2,3] Those studies, however, do not account for the increased cumulative duration of general anesthesia associated with multiple exposures to anesthesia. Therefore, it is unclear whether the worse outcome is due to repeated exposures or simply a greater total duration of anesthesia.

Methods: Postnatal day (P)7 male rats were anesthetized using isoflurane. In one group, subjects were exposed to isoflurane for 6 hours continuously. In the other group, animals were anesthetized for 3 hours on P7 and then again for 3 hours on P8, resulting in a combined total of 6 hours. A control group was included that did not undergo anesthesia. Long-term behavioral outcome was assessed weeks later using a series of associative memory tests which included various novel object recognition (NOR) tasks and an item association task (IA). Both memory tests evaluate context-specific memory and the ability to recognize objects and scents using specific contextual cues.

Results: Animals in the repeat exposure group ("Iso 3 + 3") demonstrated worse behavioral outcomes than those in the single exposure group ("Iso 6"). Iso 3 + 3 subjects were impaired in all variants of the NOR task while Iso 6 animals were only impaired in the most complex task. In the IA task, both groups were impaired relative to control when relying on proximal and distal contextual cues. Iso 3 + 3 (repeat exposure) performed worse than Iso 6 (single exposure) in the proximal contextual cue task.

Conclusion: Isofurane exposure in neonatal rats results in impaired long-term associative memory. Repeated exposure leads to worse outcome than a single exposure even when the total anesthetic duration is equivalent.

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[SNACC-3] Caveolin-1 is a Biomarker of Propofol Mediated Neurotoxicity in Developing Neurons

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Background: A wide body of evidence indicates that anesthetic exposure during synaptogenesis in the developing brain causes widespread neurodegeneration, electrophysiologic abnormalities of neuronal networks and long-term cognitive deficits. Although the mechanism by which anesthetics injure the neonatal brain is not known, GABA-A mediated excitation, NMDAR antagonism mediated excitotoxicity, aberrant cell cycle entry, mitochondrial injury and free radical mediated toxicity play a role. Work from our laboratory has demonstrated that preferential signaling of proBDNF via p75NTR leads to downstream activation of

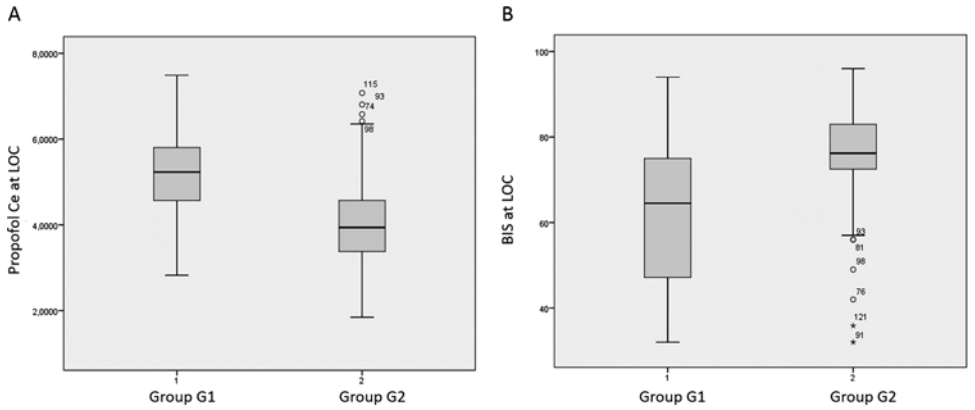

Figure 1: Data distribution for Propofol Ce (ug/ml) at LOC and BIS at LOC in Groups G1 and G2

[SNACC-57] Anesthesia Induction with Propofol and Remifentanil for Neurosurgery: Identification of a BIS Time Delay

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There is a delay in the bispectral index (BIS) related to the smoothing rate, which is approximately 5-10 seconds, according to the manufacturer[1–3] suggest longer delays, but were criticized for not using a clinical approach. The aim of this study was to evaluate the existence of

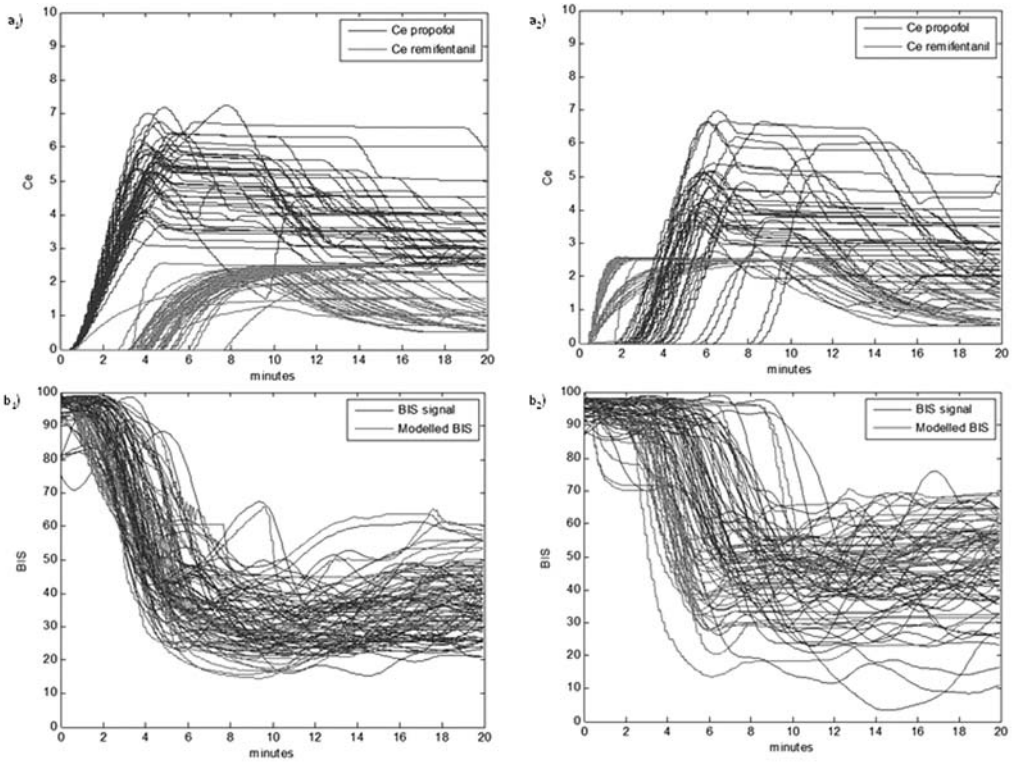

Figure 1: Site-effect concentration of propofol (Ce propofol – in mg/ml) and remifentanil (Ce remifentanil – in ng/ml), for a_1) 45 patients from G1 and a_2) 45 patients from G2; BIS signal versus predicted BIS for b_1) 45 patients from G1 and b_2) 45 patients from G2, during the induction phase of anesthesia.

a delay in the BIS response through an innovative approach using the difference between the predicted and the actual BIS in the induction of general anesthesia with propofol/remifentanil. Another aim was to analyze the delay according to two different induction protocols.
A posteriori (IRB approval) the induction data of patients scheduled for neurosurgery with 2 different anesthesia protocols were analyzed: G1– propofol infusion starts at 200 mL/h until loss of consciousness (LOC) followed by remifentanil with an effect-site concentration (Ce) target of 2.5 ng/mL; G2– remifentanil infusion starts with a Ce target 2.5 ng/mL and 1 minute after the remifentanil Ce target is achieved, propofol infusion starts at 200 mL/h until LOC. After LOC drug's infusion (TCI) are changed according to patient needs to maintain BIS at 40-60. The following data were recorded every 5 seconds, during the first 20 minutes of induction, with Rugloop®: propofol Ce (Pk-Schnider), remifentanil Ce (Pk-Minto) and BIS. These data were used to identify the pharmacodynamics (PD)[4] of each patient and to predict the BIS response. The BIS time delay was identified as the difference between the predicted response of the PD model and the actual BIS of the patient. Data are Mean ± SD. T-test was applied ($P < 0.05$).
Data from 45 patients for each group were analyzed, demographics did not differ. Propofol Ce, Remifentanil Ce and predicted BIS versus actual BIS of each patient are shown in Fig. 1, The mean absolute error (MAE) between predicted and actual BIS was of 5.8 ± 2.7 in G1 and 9.9 ± 4.4 in G2 ($P < 0.001$). Delays of 0.59 ± 0.43 minutes in G1 and 1.15 ± 0.63 minutes in G2 were identified ($P < 0.001$).
These results suggest a delay in the BIS response on average 0.59 or 1 minute, a much higher value than the announced by the manufacturer and clinically significant. This delay is similar to that suggested in other studies, but in our study we had the advantage of using real patient data. The different delay depending on the induction protocol (G1 or G2) may be related to the fact that the PK models Ke0 do not correctly predict the effect/concentration delay, or due to the inter-patient variability which can be greater than expected. The difference between groups suggests that the drug's interaction may have different magnitudes according to the protocol of induction. The results are clinically relevant: during induction BIS must be interpreted taking into account the time delay and drug infusion protocol.
References:
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[SNACC-58] Evaluation of Facial Nerve Motor Evoked Potentials Using Threshold Level Stimulation Method During Skull Base Surgery

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Background: The preservation of facial nerve function is one of the primary objectives in skull base surgery. Recently, transcranial facial nerve motor evoked potentials (Tc-FNMEP) has been used to monitor intraoperative facial nerve function. However, there are some difficulties in interpretation of waveform change due to low reproducibility of Tc-FNMEP waveform. The present study was designed to investigate the reliability of intraoperative Tc-FNMEP using threshold level transcranial stimulation during skull base surgery.
Methods: Twenty-five patients (57.5 ± 13.1 y, 8 males and 17 females) undergone elected skull base surgery using Tc-FNMEP monitoring were studied. General anesthesia was maintained by total intravenous anesthesia using propofol without neuromuscular blockade. Threshold level transcranial stimulation of Tc-FNMEP was established with minimum intensity to elicit the waveform from recording muscles. A train of 4 pulses with 500 Hz was delivered through corkscrew electrodes at C3/C4 (international 10/20 method). Subdermal needle electrodes placed in the orbicularis oculi muscle at the lateral angle of the bilateral eyes and in the orbicularis oris muscle at the bilateral angle of the mouth for recording Tc-FNMEP. MEE-1232 (Nihon Kohden, Tokyo, Japan) was used as an electrophysiological device. Significant change of amplitude was defined as more than 50% decrease compared with baseline amplitude. Facial nerve function was evaluated preoperatively and postoperatively using the House and Brackmann grading system. The reliability of intraoperative Tc-FNMEP was assessed by sensitivity and specificity to detect postoperative facial nerve dysfunction.
Results: Control Tc-FNMEP waveforms were successfully recorded in all patients. Of 25 patients, significant sustained decreases of Tc-FNMEP until the end of surgery were observed in 6 patients. Postoperative new facial nerve dysfunction or worsen facial nerve function were observe in 6 patients. Of the 6 patients with postoperative deterioration of facial nerve function, 4 patients had intraoperative significant decline of Tc-FNMEP. The sensitivity and specificity of intraoperative Tc-FNMEP to detect postoperative facial nerve dysfunction were 66.7% and 84.2%, respectively.
Conclusions: The results in this study indicated the feasibility of intraoperative Tc-FNMEP using threshold level transcranial stimulation during skull base surgery.

[SNACC-59] Assessment of Neuromonitoring Techniques in Intracranial Aneurysm Surgeries

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Introduction: Intracranial aneurysm clipping is associated with significant mortality and morbidity primarily due to ischemia in the vascular territory of the aneurysm. Surgical clipping of aneurysms is preferred when the morphology of the aneurysm does not permit endovascular coiling. Over the last 10 years intraoperative neuromonitoring (IONM) of motor evoked potential (MEP), sensory evoked potential (SSEP) and electroencephalography (EEG)- collectively, neuromonitoring, has been advocated to identify ischemic insults potentially resulting in poor outcomes. The premise being, an ischemic insult will lead to an alert, which, with corrective measures could be resolved, preventing ischemic damage. Our aim in this study is to assess the clinical value of neuromonitoring during aneurysm surgery.
Methods: After approval from Yale University IRB electronic records of all patients who were monitored with MEP, SSEP & EEG during surgical clipping of aneurysm between 2010 -14 were reviewed. Intraoperative changes in MEP, SSEP & EEG, ("alerts") as determined by the neurophysiologist, and any intervention carried out by the care team were identified. The criteria for diagnosing IOM alert was:
- EEG - decrease in amplitude and/or frequency or burst suppression.
- MEP - decrease in amplitude of the motor action potential.
- SSEP - 50% decrease in amplitude and /or 10% increase in latency.
We correlated the neuromonitoring alerts with the postoperative outcome (Glasgow Outcome Score - GOS) at 6 weeks.
Results: There were 72 patients (14 males & 58 females). In two cases though clipping was planned endovascular coiling was performed. Patient population included 46 unruptured and 26 ruptured aneurysms. Most of the aneurysms were in the anterior and middle cerebral artery territory.
Based on GOS, 61/72 patients (84.7%) had a good outcome (minimal or no neurological deficit), while 11/72 (15.3%) had a poor outcome. Of the patients with good outcomes, 19 had one or more alerts that resolved with intervention. Of the 11 patients with deficits, 3 had alerts and 8 did not.
In the entire group 22/72 (30.6%) patients had alerts (14 in EEG, 8 in MEP and 6 in SSEP). In 19/22 cases the alerts resolved after intervention and these patients had a good outcome. In the remaining 3, the alerts did not resolve and patients had significant deficits postoperatively. Among the 50 patients with no alerts, 8 had poor outcomes.
Conclusions: With the institution of IONM 84.7% patients had a good outcome. While the individual monitors by themselves were not sensitive enough when all the three (EEG, SSEP, MEP) are monitored the sensitivity of detection of intraoperative ischemia improves to 73.3% (22/30) considering the 8 cases with no alert and poor outcome. There is some chance that vasospasm or other etiologies may have played a role in the 6-week postoperative outcomes. We recommend monitoring EEG, SSEP and MEP for all intracranial aneurysm surgical clipping.