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

Jian M*, Pearn M†, Egawa J*, Head B*, Patel P*, Han R‡. **University of California, San Diego, San Diego, California, United states.* †*University of California, San Diego, San Diego, California, United states.* ‡*Beijing Tiantan Hospital, Beijing, Beijing, China.*

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

Lee B, Sall J. *University of California, San Francisco, San Francisco, CA, US.*

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

Pearn M*, Elvina D*, Patel H†, Patel P*, P B†. **University of California at San Diego, San Diego, California, United States.* †*Veterans Affairs Medical Center, La Jolla, California, United States.*

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

[SNACC-97] Blood Transfusion and Anaemia in Patients Undergoing Posterior Lumbar Interbody Fusion

Lalabekyan B*, Moss C†, Luoma A†. *Barts and the London School of Medicine, London, UK. †National Hospital for Neurology and Neurosurgery, London, UK.

Introduction: In-hospital blood transfusion is common, around 12% of inpatients in the US, and is associated with increased peri-operative morbidity and mortality in both cardiac and non-cardiac surgery. Pre-operative anaemia is also common, present in up to 30% of patients.[1,2] It is independently associated with increased 30-day morbidity & mortality after major non-cardiac surgery including infection risk,[2] which is further increased by peri-operative blood transfusion.[2,3] Currently decision to transfuse is based on a risk benefit decision with no established recommendation on thresholds. Posterior lumbar interbody fusion surgery [PLIF] is common and may be associated with haemorrhage. As with any surgical implants there is a risk of surgical site infection.

Our aim was to Establish:

[1] Mean peri-operative haemoglobin drop for PLIF.

[2] Incidence of pre-operative anaemia and peri-operative blood transfusion rate.

Association with length of hospital stay [LOS].

Methods: Retrospective electronic case-note review of all patients undergoing elective PLIF over a 2-year period. Data collected included: patient demographics, length of hospital stay, peri-operative haemoglobin drop & blood transfusion rate. Anaemia defined according to WHO criteria.[4]

Results: N = 157; median age 62 [30-83] years; incidence of pre-operative anaemia 14.6%; overall transfusion rate 15.9%. Mean haemoglobin drop 31.27 [14.6] g/L. [table 1].

Anaemic patients were more likely to receive a blood transfusion [$P = 0.0132$ Fishers Exact] but there was no significant difference in LOS between patients with pre-operative anaemia and no anaemia. Blood transfusion was associated with significantly increased LOS [$P = 0.0001$ unpaired t-test].

No significant difference in mean [SD] haemoglobin drop between 1-level and more than 1-level PLIF [30.86 [14.3] g/L versus 31.98 [15.3] g/L]. No difference in incidence of blood transfusion or LOS between the groups.

Conclusion: Pre-operative anaemia is common in patients undergoing PLIF and associated with increased blood transfusion with subsequent increased LOS, in keeping with published data. Mean haemoglobin drop is significant but similar for single and multi-level PLIF, and should be considered when preparing patients for surgery, particularly with the lack of clarity on transfusion thresholds. Early identification and treatment of anaemia could prevent transfusions and the resultant risk of increased morbidity and mortality. It is essential to ensure that patients and clinicians are fully informed of the risks associated with anaemia & blood transfusion to improve patient safety, and to ensure decisions are shared.

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	All patients N=157	1-level PLIF N=101	> 1-level PLIF N=56
Patient demographics:			
•Median age [range] years	62 [30-83]	62 [32-82]	60 [30-83]
•Gender	61M:96F	46M:55F	15M:41F
•Mean [SD] length of stay, days	8.24 [7.86]	8.1 [8.99]	8.5 [5.8]
Mean [SD] pre-operative Haemoglobin g/L	135.62 [17.9]	136.46 [19.5]	134.13 [14.9]
Mean [SD] haemoglobin drop g/L	31.27 [14.6]	30.86 [14.3]	31.98 [15.3]
Blood transfusion:			
• Incidence	15.9%	14.8%	17.9%
• % patients anaemic*	34.8%	33.3%	37.5%
• Mean [SD] length of stay**	15.04 [12.47]	17.6 [17.1]	11.2 [5.29]
Anaemia:			
•Incidence	14.6%	14.8%	14.3%
•Mean [SD] length of stay days***	9.91 [8.74]	10.6 [10.77]	8.62 [4.69]

Table 1: Comparison between groups for anaemia and blood transfusion
*P = 0.0132 for increased rate of blood transfusion if anaemia pre-operatively
** p= 0.0001 for difference in LOS between transfused and non-transfused
*** p > 0.05 for difference in LOS between anaemic and non-anaemic patients

[SNACC-98] A Survey on the Practice of Anesthesia Induction and Loss of Consciousness Assessment

Ferreira A*, Nunes C†, Gabriel J*, Lobo F‡, Amorim P‡. *Faculdade De Engenharia Da Universidade Do Porto, Porto, Portugal. †Universidade Aberta and Centro De Investigalcao Em Anestesiologia Chp, Porto, Portugal. ‡Centro Hospital Do Porto, Porto, Portugal.

Propofol is the mostly used drug for induction in all cases or maintenance in total intravenous anesthesia. For induction it is given as a manual bolus based on the patient's weight. TCI systems are now increasingly used, allowing information regarding predicted plasma and brain concentrations and the administration of propofol by setting a concentration target. Induction and maintenance with propofol, should be performed avoiding excessive anesthesia. Knowledge of pharmacokinetics (effect of bolus velocity, magnitude of overshooting and relation to velocity) and pharmacodynamics (fall in blood pressure, usage and correct interpretation of BIS) is important for better titration of anesthesia. We conducted a survey to assess how Portuguese anesthesiologists use propofol to induce and maintain general anesthesia, how they use TCI, interpret BIS, identify overshooting and assess loss of consciousness (LOC).

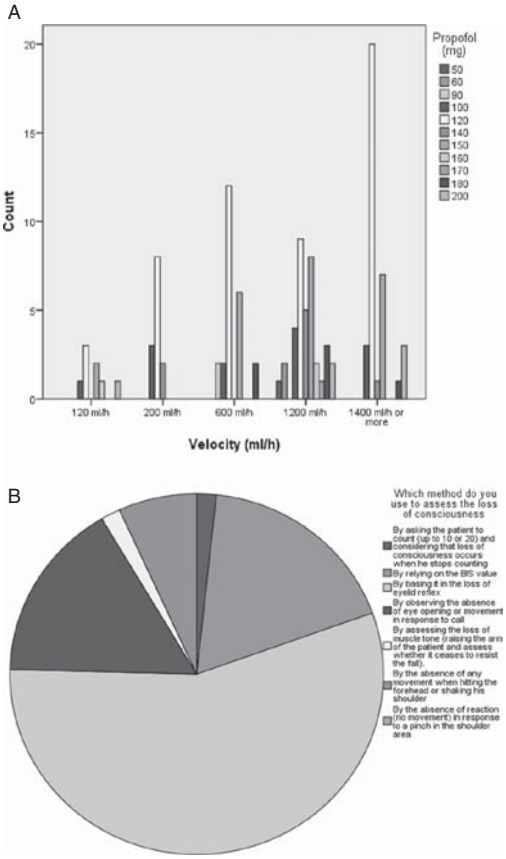

Figure 1: **A** - Response distribution regarding the chosen dosage for propofol and the chosen infusion velocity to achieve loss of consciourness.
B - Response distribution regarding the assessment method for the moment of loss of consciousness.

Anesthesiologists working at 10 large public hospitals in Portugal were sent an email requesting them to answer an on-line survey. IRB approval was obtained. Preceding the questions, a clinical scenario was presented: a male patient (50 y, 60 kg, 160 cm, ASA I), unpremedicated is ready to undergo general anesthesia and tracheal intubation for a laparotomy procedure to perform a cholecystectomy. 0.15 mg of fentanyl were administered 3 minutes before induction with 1% propofol using a 20 cc syringe. The anesthesiologist is at the bedside, pre-oxygenating, monitoring and instructing a nurse administering the drugs through an IV line inserted in the back of the patient's hand. Standard monitoring is ASA and BIS. A total of 118 anonymous responses were received and some of the results are summarized.

In the scenario above, 44% of anesthesiologists chose 120 mg as the dosage of propofol they would administer to induce LOC and 32% chose 1200 mL/h as the infusion velocity (there was no significant correlation between variables) (Fig. 1). The majority (56%) assess LOC by the loss of eyelid reflex, 18% rely on the BIS and 16% on the absence of movement. A BIS below 60 was chosen by 38% as the value at which patients, on average lose consciousness (Fig. 1). When asked about the use of TCI of propofol (PK Schnider), 22% perform induction by setting a fixed brain target, 4% by stepwise increasing the brain target, 9% by a fixed plasma target, 3% by stepwise increasing the plasma target, 24.6% use the TCI-View mode and 36.4% never used TCI. When asked to choose a figure for the magnitude of the effect site overshooting of propofol if given with the infusion velocity chosen for the induction, a significant positive Spearman correlation between the chosen infusion velocity and the chosen overshooting was found ($R = 0.249$, $P < 0.01$). This survey showed a wide variation in the way propofol is used and in the interpretation and knowledge of pharmacology.

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[SNACC-99] Factors Affecting the Outcome of Patients Undergoing Surgery for Craniopharyngioma

Mitra R, Prabhakar H, Rath G, Bithal P. *All India Institute of Medical Sciences, New Delhi, Delhi, India.*

Introduction: The incidence of craniopharyngioma is stated around 1.3 per million person-years; the incidence is higher in India with 10.2%. This study was conducted to determine the perioperative factors that affect the outcome of patients undergoing surgery for craniopharyngioma. The primary outcome was duration of hospital and intensive care unit (ICU) stay and Glasgow outcome scale (GOS) at discharge. The secondary outcome was the quality of life (QOL) at 3 month and 6 month after discharge from hospital.

Methods: All patients aged 5 year and above of either sex, scheduled for elective craniopharyngioma surgeries from 1st April 2014 to 31st March 2015 were included in the study. The demographics, baseline characteristics (admission Glasgow coma scale, tumor size, hormonal status, location, hydrocephalus, hypothalamic involvement), intraoperative data (anesthesia and surgery related), GOS at discharge, and postoperative QOL assessed using the Health Utility indices (HUI-2/3) for a period up to 6 months after surgery were collected. Appropriate statistical analysis was done. Data are presented as median [Range], mean (SD) or number (%).

Results: Twenty two patients were included in the study. The duration of hospital and ICU stay were 17 days (6-64) and 3.5 days (1-25), respectively. The GOS at discharge was 5 (2-5). There was no in-hospital mortality. The baseline prolactin level and involvement of hypothalamus affects GOS at discharge. The quality of life at 3rd and 6th month did not change significantly when compared to baseline (i.e. health status of patient 1 wk prior to admission to hospital). No factor affecting the QOL could be identified.

Conclusion: None of the demographic or perioperative factors affecting the QOL of patients with craniopharyngioma could be identified. Larger series may be studied for definitive outcomes.

[SNACC-100] Awake Craniotomy with Intraoperative MRI (iMRI): Our Anaesthetic Experience in a 1.5T iMRI Integrated Surgical Suite

John R*, Appleby I†. **National Hospital for Neurology and Neurosurgery, London, United Kingdom. †National Hospital for Neurology an Neurosurgery, London, United Kingdom.*

Background: To help maximize the resection of lesions located in eloquent cortex and preserve function, patients can undergo awake craniotomy with cortical mapping, or intraoperative MRI surgery.[1–3] There has been little experience combining these two techniques in the United Kingdom.

Objectives: We report our anaesthetic experience of combining awake craniotomy with intraoperative brain mapping within an integrated 1.5 T intraoperative magnetic resonance imaging (iMRI) suite.

Methods: From a prospective database we identified all patients who had undergone awake craniotomy procedures with cortical mapping in the integrated iMRI suite. We evaluated how these two modalities were integrated, and what impact this combined technique had on safety, workflow, extent of surgical resection and total operative time.

Results: Between February 2015 and April 2015, five patients (3 male and 2 female patients; age 30-48; mean 41 y) with lesions in, or adjacent to, eloquent cortex underwent awake craniotomies with iMRI surgery. Two patients had right sided lesions and three had left sided lesions. The "asleep-awake-asleep" technique with a laryngeal mask airway was used in all patients. Scalp blocks were administered by the surgeon performing the craniotomy. Anaesthesia was maintained using either sevoflurane with a remifentanil infusion (3/5) or twin propofol/remifentanil infusions (2/5). All patients had two intraoperative scans, with the mean time per scan being 29 minutes (range, 20-40 min). During the intraoperative scanning phase, the anaesthetic consultant was always present in the MRI suite. The mean surgical time was 7.6 hours (range, 6.5-10 h) and the extent of surgical resection was > 95% in all five cases. One patient had an intraoperative seizure, but no other complications were noted in our case series.

Conclusions: Awake craniotomy and direct cortical stimulation can be performed safely and effectively within a 1.5T iMRI suite. Our preliminary case series is the first from the United Kingdom, and shows that both volatile and intravenous anaesthesia are well tolerated in this setting. This emerging technique however prolongs the total surgical time significantly. Careful patient selection and preparation is therefore crucial.

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[SNACC-101] The Effect of Remifentanil Infusion on Successful Cortical Mapping During Awake Craniotomies

Hammer M*, Kosky J*, Hemmer L*, Bebawy J*, Tate M*, Gupta D†, Koht A*. **Northwestern Memorial Hospital, Chicago, IL, United States. †Duke University, Durham, NC, United States.*

Introduction: Awake craniotomy is an increasingly common surgical modality used to resect masses in and around the eloquent and motor areas, and ensuring patient comfort and cooperation during the procedure is paramount. Many studies have been published that suggest successful anesthetic techniques for optimizing conditions during cortical mapping. However, these studies generally discontinued sedation during the mapping period, out of concern that these medications interfere with the accuracy of mapping the eloquent cortex. In this observational crossover study, we assessed the ability to perform cortical mapping via cortical stimulation during remifentanil infusion.

Methods: All patients received scalp blocks with sedation upon arrival to the operating room. A sedation regimen of remifentanil 0.03-0.18 mcg/kg/min and propofol 5-25 mcg/kg/min was subsequently started, titrating dosages to maintain a respiratory rate of 8-12/minute. When the time for cortical mapping approached, infusions were discontinued for at least 15 minutes prior to allow washout. After completion of stimulation for cortical mapping, remifentanil was restarted for five minutes at 0.1 mcg/kg/min (if the maintenance infusion used before was at 0.1 mcg/km/min or higher). If the maintenance infusion of remifentanil was less than 0.1 mcg/kg/min, the starting infusion during this study period was adjusted down to that level. After five minutes of the infusion, the dose was decreased to half the initial study infusion for five more minutes to achieve a patient-specific steady state concentration. The neurosurgeon then repeated sensory, motor and speech mapping to the previously labeled cortical areas. We examined the ability to gain the same responses during this time (i.e., remifentanil infusion study period).

Results: Thirteen subjects successfully completed the study, with a total of 119 stimulations that were repeated after the remifentanil infusion was restarted. Three patients were dropped from the study due to intraoperative complications (seizure or dysphagia). Sensory mapping was