Clonidine versus Midazolam Pre-medication and Post-operative Negative Behavioural Changes in Younger Children: A Randomized Controlled Trial

Zickerman C, Hult AC, Hedlund L, et al. Anesth Analg 2022;135(2):307-15

This randomised controlled trial found premedication with oral clonidine is not superior to midazolam at reducing negative behaviour change after day case ENT surgery. Midazolam was associated with significantly lower pre-induction anxiety than clonidine.

***Population**:* 121 children aged 24 to 95 months old undergoing elective day case ENT surgery at a single centre in Sweden
***Intervention*:** 4 mcg/kg-1 oral clonidine 60 minutes before anaesthesia
Comparator: 0.5 mg/kg-1 oral midazolam 30 minutes before anaesthesia
***Primary Outcome*:** Relative risk of negative behaviour change on post hospital behaviour questionnaire

Primary outcome: Rate of negative behaviour change was not significantly different between clonidine (n=12/59, 20.3%) versus midazolam (n=7/56, 12.5%), odds ratio 1.39, 95%CI 0.75-2.58, two tailed p=0.32. Secondary outcome: Pre-induction anxiety measured on a modified Yale Anxiety Scale. Clonidine was associated with high pre-induction anxiety more often than midazolam (n= 43/59, 71% versus n=12/56, 21%, p<.001).

This double blind parallel randomized controlled trial does not demonstrate superiority of clonidine as premedication for the prevention of negative behaviour change and midazolam remains a better anxiolytic premedication. Investigators also demonstrated how frequently negative behaviour change occurs following elective surgery (12.5-20.3%), and despite premedication in both groups the incidence of high pre-induction anxiety was between 21-71%. These findings should be borne in mind during preoperative consent discussions.

There are several strengths: a diversity of participants with respect to socioeconomic status, clear protocols for perioperative analgesia and minimal attrition. Only one participant was lost to follow up and five participants excluded post randomization (out of 121 randomised participants). A limitation was that investigators did not perform baseline behavioural measurements although there is no reason to expect between comparator group differences in this randomised study. Investigators also excluded ASA III–IV patients, which would represent a group more likely to receive pre-medications for other reasons and likely missed those in whom to most easily demonstrate benefit. Lastly, they set an ambitious superiority treatment effect of 25% relative risk reduction.

This study had a neutral primary outcome finding that clonidine was not superior to midazolam as a premedication for the purpose of minimising postoperative negative behaviour changes. It also found a significant association between lower pre-induction anxiety with midazolam compared to clonidine.

Reviewed by Dr. Matthew Luney

Neurocardiovascular coupling in congenital diaphragmatic hernia patients undergoing different types of surgical treatment

Hendrikx D, Costerus SA, Zahn K, et al. Eur J Anaesthesiol 2022;39(8):662-72

This European multicentre prospective observation cohort study of cerebral oximetry (NIRS) and electroencephalography (EEG) during congenital diaphragmatic hernia (CDH) repair compared patients' physiologic responses to surgery in theatre under sevoflurane to repair in the intensive care unit with midazolam.

It is difficult to separate the consequences of requiring anaesthesia as a neonate from sequelae of the pathophysiologic indication for surgery. What is known is that impaired cerebral blood flow is injurious to the developing brain. The authors hypothesized that by creating a computational model that integrates neurophysiological, cardiac, and cerebrovascular monitoring values they can arrive at a more complete understanding of neonatal cerebral blood flow under anaesthesia. They termed this neurocardiovascular graph connectivity.

Neonates undergoing CDH repair had NIRS, EEG, routine physiologic monitoring (SpO2, mean arterial pressure (MAP), heart rate) and anaesthetic drug delivery recorded. Investigators then modelled the relationship between these variables using a branch of statistics called transfer entropy. In simple terms it analyses the predictability of a signal based on another signal.

In this study investigators describe the relationship between the neurophysiologic and cardiovascular monitors, and the anaesthetic agents whilst adjusting for patient characteristics, surgical approach, and other physiologic parameters. Sevoflurane and midazolam groups received fentanyl and an aminosteroid neuromuscular blocking agent, a subgroup on VA-ECMO also received a continuous morphine infusion.

Thirty-six neonates who underwent CHD repair had data available for analysis. The primary outcome of neurocardiovascular graph connectivity demonstrated sevoflurane for thoracoscopic repair was associated with the largest reduction in connectivity. This agrees with previous work in adults which compared the effects of inhalational and intravenous anaesthesia. Most reassuringly investigators demonstrated that mean arterial pressure remained correlated with cerebral oximetry throughout the cases studied suggesting that cerebral autoregulation was not impaired with either technique. The limitations of the study include the observational design with the potential for bias from unmeasured confounding and the absence of any neurodevelopmental follow up. The study was also focused on a single operative group which may impede generalisability.

In summary, for neonates undergoing congenital diaphragmatic hernia repair, sevoflurane was associated with more disruption to the relationship between the systems for cerebral blood flow regulation than midazolam, however neither agent was associated with impaired cerebral autoregulation in this cohort study.

Reviewed by Dr. Matthew Luney

Ultrasound-guided caudal blockade and sedation for paediatric surgery: a retrospective cohort study

P. Opfermann, F. Kraft, M. Obradovic et al. Anaesthesia 2022; 77: 785-94

This is a single-centre retrospective cohort study of children ≤15 y that underwent caudal anaesthesia with sedation as their primary anaesthetic plan for general and urological surgery.

It includes 2547 cases conducted at a tertiary centre in Vienna from 2014- 2020 and reports success rate, complications and reasons for failure. Sedation technique included a combination of midazolam premedication, propofol bolus for conduct of caudal, followed by infusion of propofol 5mg/kg/h for maintenance with spontaneous ventilation and non-instrumented airway. Caudal technique is described, with a supplementary video, using a combination of landmark and real time ultrasound guidance "3-handed technique" and standardised dosing regimen. End-tidal CO2 monitoring was used with oxygen. Data was collected from the comprehensive electronic systems of the hospital, and validated by consultant anaesthetist investigators.

The primary outcome of success rate- whether the initial caudal/sedation plan had been followed, or if general anaesthesia with airway instrumentation had been required- was 95%. Complications included 9 accidental spinal anaesthetics and 39 respiratory events. The most common reason for conversion to general anaesthesia was pain-related: 83 cases (3.2%). From multiple logistic regression high body weight and more proximal surgery was associated with higher failure rates, and prematurity was associated with increased respiratory events.

This article reports acceptable success rate in a technique which can avoid general anaesthesia and the associated potential risk of neurocognitive problems, reduces use of volatile anaesthetic agents and opioid analgesia with the associated side effects. It cautions use of the technique in older age groups and mid-abdominal surgery. The rate of spinal anaesthesia appears high compared to other studies and may be attributable to training or better recognition of the event. As a single site study design it cannot confirm whether these findings can be replicated in other centres and the impact is limited by being observational and subject to retrospective bias, which lessens data quality despite careful validation.

Reviewed by Dr. Anna Ratcliffe

Perioperative opioid use in paediatric inguinal hernia patients: a systematic review and retrospective audit of practice.

Hageman IC, Tien MY, Trajanovska M, et al. Journal of Pediatric Surgery 2022; 57: 1249-57

This article combines a systematic review of prescribing and administration practice of opioids for paediatric inguinal hernia patients, with a retrospective single-centre audit of practice at The Royal Children's Hospital (RCH) in Melbourne.

The systematic review included 15 articles from 2009-2019, 12 were RCTs, with a total of 1166 patients. The primary outcome was total opioid administration in the first 24h postoperatively. There was wide variation in practice; between 3% and 100% patients were prescribed postoperative opioids, with a 5-fold range in dosing (0.07-0.35mg/kg oral morphine equivalent mean dose). Adverse events were reported in 11/15 articles and included vomiting, nausea, sleepiness, itch, urinary retention, bradycardia. Serious adverse events such as respiratory depression are not mentioned, nor are long-term outcomes such as persistent use.

The audit included 150 children <18y who underwent open inguinal hernia repair between May and December 2019 at RCH. Data was collected from electronic databases, and included opioid administration in the postoperative period before, and on discharge from hospital. 26/150 (17%) received postoperative opioids, 30/150 (20%) received intraoperative opioids. 67% received no opioids during their admission. No patients received a discharge prescription of opioids. Adverse events were not reported. Older age, female sex and absence of regional anaesthesia were shown to be statistically associated with increased opioid use, but the small numbers limits findings.

The article addresses an important topic; opioids are associated serious adverse perioperative events. Opioid stewardship is very topical and there is emerging evidence that poor postoperative prescribing practice results in long-term misuse in particular in older children. There appears to be lack of standardisation over postoperative opioid prescribing despite various guidelines, which may be due to paucity of evidence, over-use, or under-analgesia, or a number of patient and procedural factors, and further work is required to understand this.

Reviewed by Dr. Anna Ratcliffe

Risk Factors and Consequences of Acute Kidney Injury After Non-cardiac Surgery in Children

Hawkins J, Mpody C, Corridore M, et al Anesthesia & Analgesia: Sept 2022 135 (3): 625-632

Acute kidney injury (AKI) remains a significant contributor to peri-operative morbidity and mortality.

This was a retrospective multi-centre cohort study on post-operative acute kidney injury (AKI) in children undergoing non-cardiac surgery. The study cohort was taken from the American College of Surgeons National Surgical Quality Improvement Program Pediatric (ACS NSQIP), this is a paediatric database of surgical data from multiple participating sites. 257, 439 patients were identified between 2012 and 2018 that underwent an inpatient non-cardiac surgical procedure.

In order to identify independent risk factors for AKI, multivariable logistic regression was used. Acute renal failure was defined as new haemodialysis, ultrafiltration or peritoneal dialysis in patients previously not on any of the above and progressive renal insufficiency was defined as "a rise in creatinine of >1 mg/dL from preoperative value, without any requirement for dialysis."

The prevalence of AKI rate post-operatively was 0.1% (0.09- 0.11, 95% CI). The risk factors most strongly associated with AKI were operating times >140mins (aOR 4.32; 2.73- 6.85, 95% CI), the pre-existence of a haematological disorder (aOR 4.18; 2.96- 5.91, 95% CI) or sepsis (aOR 3.43; 2.42–4.87, 95% CI). Others important risk factors were ASA ≥ III, ventilator dependence, use of steroids inotropic support. Patients with AKI had a ten-fold higher 30-day mortality and were three times more likely to have a prolonged length of stay.

Identifying high risk patients pre-operatively could help clinicians potentially mitigate these risks and target interventions to more vulnerable patients. The authors suggest interventions such as careful fluid balance, attention to adequate volume status and perfusion pressures, avoiding nephrotoxic drugs and perioperative hyperglycaemia and limiting surgical times for those particularly at risk of AKI.

This is a very large data set and therefore gives important insights into risk factors and mortality.

Reviewed by Dr. Leda Lignos

Association of Blood-Based Brain Injury Biomarker Concentrations with Outcomes After Pediatric Cardiac Arrest

Fink EL, Kochanek PM, Panigrahy A, et al. JAMA Netwok Open. 2022 Sep 1; 5(9): e2230518.

Blood-based brain injury biomarkers have recently gained traction for their use in neurological outcome prediction. GFAP (glial fibrillary acidic protein and UCH-L1 (ubiquitin carboxyl-terminal esterase) have been approved by the US- FDA for prediction of outcome in traumatic brain injury. In the adult population several studies have identified several different biomarkers which could aid prognostication following cardiac arrest.

This prospective multi-centre cohort study looked at GFAP, UCH-L1, tau and NfL (neurofilament light) in blood on days 1,2 and 3 after cardiac arrest and their association with an unfavourable outcome 1 year after cardiac arrest. Unfavourable outcome was defined as death or survival with disability – classified by the Vineland Adaptive Behaviour scale score, third edition (VABS-3). This uses communication, daily living, socialization and motor skills to generate an age-corrected standard score. A score of <70 was deemed an unfavourable outcome and >70 favourable.

Patients were recruited from 14 PICUs in the US, ages ranged from 48hrs to 17 years and excluded from the study if they had a pre-cardiac arrest score on the Paediatric Cerebral Performance Category scale of 4-6 (indicating pre-existing severe disability). In and out of hospital cardiac arrests were included, with any length of chest compressions. The final sample size following ineligibility and exclusions was 120 children. Samples were analysed by technicians blinded to patient clinical details externally from recruiting centres.

In summary, 70 children had a favourable outcome and 50 unfavourable (43 of these were death). The concentrations of the 4 measured biomarkers were all higher in days 1,2 and 3 in children with an unfavourable outcome. Following adjustment for factors such as unwitnessed event and high risk of death score at admission their results were still significant. NfL on day 2 and 3 appeared to be the most sensitive out of the biomarkers for prediction of an unfavourable outcome at 1 year.

The authors comment on limitations of their study being the high proportion of ineligible patients from a potential larger group and the absence of more detailed neurodevelopmental outcomes which could have yielded even more compelling conclusions regarding biomarkers. Their results do however give clear signals about the utility of blood-based biomarkers both for prognostication and potentially guiding future research on targeting interventions to certain population groups.

Reviewed by Dr. Leda Lignos

Edited by Dr. Kira Achaibar