Short-term Outcomes in Infants after General Anesthesia with Low-dose Sevoflurane/Dexmedetomidine/Remifentanil versus Standard-dose Sevoflurane

The TREX Trial

Saynhalath R, Disma N, Taverner FJ, von Ungern-Sternberg BS, Andropoulos D, Ng AS, Shields BB, Izzo F, Lee-Archer P, McCann ME, Montagnini L, Kuppers B, Lenares E, Sheppard S, de Graaff JC, Lee KJ, Wang X, Szmuk P, Davidson AJ, Skowno JJ; TREX (Trial Remifentanil DEXmedetomidine) Consortium. Short-term Outcomes in Infants after General Anesthesia with Low-dose Sevoflurane/Dexmedetomidine/Remifentanil versus Standard-dose Sevoflurane (the TREX Trial). Anesthesiology. 2024 Dec 1;141(6):1075-1085. doi: 10.1097/ALN.0000000000005232. PMID: 39283983.

Summary

This is a secondary analysis comparing the two treatment groups in The Trial Remifentanil DEXmedetomidine (TREX) trial looking at early perioperative results. TREX, which is ongoing, was designed to determine whether, in children less than 2 years of age having anesthesia expected to last 2 hours or longer, low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia (LD-SEVO) is superior to standard-dose sevoflurane anesthesia (STD-SEVO) in terms of global cognitive function, as assessed at 3 years of age. This secondary analysis presents and compares short-term perioperative outcomes from the TREX trial such as the prevalence of intraoperative hypotension, bradycardia, light anesthesia events, postoperative pain scores, time to recovery, and morbidity and mortality.

TREX is a randomized active controlled, parallel group, assessor blinded, multicentre, superiority trial that was performed in 20 centres in Australia, Italy, and the United States between August 2017 and April 2023. 455 infants less than 2 years of age and expected to undergo general anesthesia for at least 2 hours were enrolled. They were randomized between the LD-SEVO and STD-SEVO treatment arms.

The results show there was statistically significant less hypotension and more bradycardia in the LD-SEVO arm compared to the STD-SEVO arm. There were more patients with episodes of light anesthesia (89 vs. 4) and protocol abandonments (1 vs. 0) in the LD-SEVO arm. Time from eye opening to post-anesthesia care unit discharge was similar in both arms, as were morbidity and mortality. One patient in each arm suffered a life-threatening event, but neither suffered long-term sequelae.

The authors conclude that these early peri-operative results suggest that in children included in the study the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia technique and the standard sevoflurane anesthesia technique are broadly clinically similar, with no significant evidence to support choosing one technique over the other.

Commentary

Concerns about anesthesia-induced developmental neurotoxicity from anesthetic agents persist due to findings in animal models, but the few human studies available show conflicting results. The TREX trial is a large RCT looking at global cognitive function in children after having had anesthesia comparing two different anesthesia techniques. The primary outcomes of the TREX trial have not yet become available. However, the findings from this secondary analysis show that from a short term clinical point of view the two techniques are broadly similar with no clear evidence that one is superior. This will of course be relevant if the primary outcome of the TREX trial favours the LD-SEVO technique.

Even though there were more 'light anaesthesia' episodes in the LD-SEVO arm, these did respond well to the described increases in suggested drug dosing allowed within the protocol. So they did not need a change of anesthetic technique. Furthermore, in the STD-SEVO arm for more than half of the patients the incidence of 'light anaesthesia' was not recorded (not part of the initial data collection) so the difference in incidence might be less than suggested on the recorded data.

There are several limitations apparent in this study. The degree of hypotension was deemed not clinically significant in either arm. However, there is no established definition for hypotension in infants (under anesthesia) and no clear correlation between treatment of intra-operative hypotension and outcomes. A similar problem exists with regards to the incidence of bradycardia as it is unclear what the clinical importance is of these episodes. Also, for the majority of bradycardia episodes data on rescue treatment administered was missing.

The authors further note that the power calculation was based on the primary outcome, not these short term outcomes. Additionally, they haven't looked at differences in surgical suitability between the two anaesthetic techniques. Despite this there were a wide range of procedures included in both arms and only in one patient was the anaesthetic technique changed in a way that was not accepted within the study protocol. This shows that clinically surgical suitability was not a problem.

Data collection was limited to discharge from the PACU so any adverse events after this time cannot be compared, including the possibility of later hyperalgesia secondary to remifentanil infusion.

The study is applicable to our practice and population in Australia and New Zealand. Not only was a significant part of the participating patients recruited in Australian centres, the anesthetic techniques compared are or can easily be adapted as routine practice.

Overall, this study shows that from a short term peri-operative perspective it seems there would be no significant negative effects of implementing the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia technique in clinical practice if the

primary outcome of TREX would show a favorable outcome in terms of global cognitive function at 3 years of age in this treatment arm.

Reviewed by Dr Roeland Passier

Consensus on decommissioning piped nitrous oxide from UK and Ireland operating theatre suites

A rational approach to an increasingly ignoble gas

Southall P, Shelton C, Chakera A. Consensus on decommissioning piped nitrous oxide from UK and Ireland operating theatre suites: a rational approach to an increasingly ignoble gas. Anaesthesia. 2024 Dec;79(12):1274-1279. doi: 10.1111/anae.16407. Epub 2024 Aug 7. PMID: 39108217.

Summary
This editorial summarises the context and evidence for the release of the July 2024 Consensus statement of the Association of Anaesthetists, Royal College of Anaesthetists, College of Anaesthesiologists of Ireland, Association of Paediatric Anaesthetists of Great Britain and Ireland and the Obstetric Anaesthetists' Association, that piped nitrous oxide (N20) should no longer be considered essential and that healthcare institutions should decommission their piped supply systems and/or where nitrous oxide is deemed still to be clinically required, move to more efficient methods of supply, such as cylinders.

The consensus statement recommendations are that N20 should no longer be considered essential in modern practice, and that pipeline supply is not essential. Timely decommissioning of pipelines, with cylinder use where required is suggested, and Trusts are advised to liaise early with suppliers, so that supply to areas still requiring N20 use is uninterrupted.

Nitrous oxide use, pharmacokinetics and environmental issues are described in detail as well as the reported leakage of >90% at many European centres. The authors include a brief discussion of its use in modern practice and describe a stepwise approach to N20 mitigation. The editorial also considers the challenges to implementation, and other considerations including nitrous "cracking" technology, and the issue of industry venting.

Commentary
This editorial covered the many challenging aspects of decommissioning nitrous oxide pipelines along with guidance on why this is required and how to undertake the process. It had interesting points on the importance of medical body support, strategies for success and discussion points on environmentally friendly anaesthesia, changes to modern practice and future considerations.

While the editorial focuses on European/UK based decommissioning, it should be noted that this is timely, and highly relevant to Australasian practice.

Reviewed by Dr Louisa Swain

International multiinstitutional external validation of preoperative risk scores for 30 day in hospital mortality in paediatric patients

Tangel VE, Hoeks SE, Stolker RJ, Brown S, Pryor KO, de Graaff JC; Multicenter Perioperative Outcomes Group (MPOG) Perioperative Clinical Research Committee. International multi-institutional external validation of preoperative risk scores for 30-day in-hospital mortality in paediatric patients. Br J Anaesth. 2024 Dec;133(6):1222-1233. doi: 10.1016/j.bja.2024.09.003. Epub 2024 Oct 29. PMID: 39477712.

Overview
This is an external validation study of two patient-specific paediatric preoperative risk scores for 30-day in-hospital mortality.

Methods
The Pediatric Risk Assessment (PRAm) score and the intrinsic surgical risk (ISR) score were selected by the investigators as the two patient-specific risk scores to be externally validated, as these scores had previously been identified as having a low risk of bias.

Both the PRAm score and the ISR score were developed using data from the American College of Surgeons (ACS) National Surgical Quality Improvement Program-Pediatric (NSQIP-P) database (from 2012-2013 and 2012-2016 respectively).

This study aimed to externally validate both scores using retrospective observational data from the Multicentre Perioperative Outcomes Group (MPOG) registry, collected from 56 hospitals in the USA and the Netherlands between 2015 and 2020. Cardiac and diagnostic imaging procedures were excluded. The primary outcome was 30-day in-hospital mortality. The 30-day in-hospital mortality for the MPOG dataset was 0.14%, significantly lower than in the derivation NSQIP-P datasets (0.4% and 0.34%).

The two risk scores were assessed for:
- Discrimination (ability to separate survivors from non-survivors)
- Calibration (how accurately predictions matched the observed 30-day in-hospital mortality rates)
- Clinical utility/decision analysis (the extent to which the risk scores actually affect clinical decisions)

Results

• The ISR score exhibited better discrimination and specificity than the PRAm score, but both scores resulted in large numbers of false-positive cases (i.e. predicted death but patient survived). The superior performance of the ISR score was largely due to its inclusion of the ASA Physical Status score. Both scores exhibited substandard discrimination compared with the original studies.

• Calibration metrics were deceptively favourable for both scores because the vast majority of cases had low probabilities of mortality (81.4% of cases were ASA PS 1 or 2; 30-day mortality in the MPOG dataset was 0.14% compared with 0.4% and 0.34% in the NSQIP-P datasets of the original studies). This meant that predicting that a patient would not die would be correct in the vast majority of cases. Both scores were poorly calibrated at higher probabilities of mortality (mortality was overestimated for these cases).

• Decision curve analysis showed that neither score was useful in supporting clinical decision-making, except at very low probabilities of mortality.

Discussion

Risk scores can be clinically useful if they quantify risk better than clinician judgement alone. For example, they can help to guide informed perioperative decision-making and communication with patients and families or identify high-risk patients who may benefit from the allocation of additional resources.

Risk scores are well established in the adult preoperative setting. Several preoperative risk scores are available to predict perioperative mortality in children undergoing noncardiac surgery, but none have undergone multicentre external validation.

External validation is the testing of a risk score on a different set of patients to determine whether the score performs to a satisfactory degree. Risk scores should not be recommended for general clinical use without satisfactory external validation.

This external validation study found that the PRAm and ISR scores performed poorly when compared with their performance in the original internal validation studies. This may be at least partially explained by:

• important case mix differences between the NSQIP-P and MPOG datasets
• difficulties in reproducing all of the data elements used in the original studies: importantly, the investigators could not recreate the measure of intrinsic surgical risk used in the ISR score due to differences in data nomenclature. As a result, only the patient-specific variables of the ISR score were used in this analysis.

Interestingly, the superior performance of the ISR score in sicker patients was largely driven by a subjective clinical assessment (ASA Physical Status score), suggesting it adds little to clinical judgement in higher-risk patients.

Take home points

The overall performance in this study of the PRAm score and the ISR score, which were assessed as the best available risk scores, suggest they are unlikely to be clinically useful in predicting the rare outcome of 30-day mortality in a diverse paediatric noncardiac surgery population.

This study also calls into question the role of preoperative risk prediction scores in modelling the rare outcome of 30-day mortality in paediatric patients.

Reviewed by Dr Andrew Hughes

Analgesic efficacy and safety of erector spinae plane block in pediatric patients undergoing elective surgery

A systematic review and Meta-analysis of randomized controlled trials

Park SM, Kim HS, Lim BG. Analgesic efficacy and safety of erector spinae plane block in pediatric patients undergoing elective surgery: A systematic review and Meta-analysis of randomized controlled trials. J Clin Anesth. 2024 Nov;98:111575. doi: 10.1016/j.jclinane.2024.111575. Epub 2024 Aug 10. PMID: 39128258.

Summary

This systematic review and meta-analysis compared analgesic efficacy and safety between erector spinae plane block (ESPB) and controls in paediatric surgical patients. The primary outcome analysed was cumulative opioid consumption. Secondary outcomes analysed were pain score, intra-operative opioid consumption, parental satisfaction, time to extubation, post-operative nausea and vomiting, and the incidence of itch and hypotension.

The authors utilised a comprehensive search strategy and identified 17 randomised controlled trials, comprising 919 participants. The participants underwent a variety of thoracic, abdominal, and hip surgical procedures. Control groups included those who received no blocks or sham blocks, as well as those receiving blocks other than ESPB.

The study demonstrated a statistically significant difference favouring ESPB when comparing cumulative opioid consumption after surgery (their primary outcome). A statistically significant difference favouring ESPB was also demonstrated for the time to first request for post-operative analgesia, the need for rescue analgesia, pooled pain scores, and intraoperative opioid consumption.

Additional subgroup analyses were performed, separating the control group into those who received no blocks, or those who received blocks other than ESPB. In these analyses statistically

significant differences favouring ESPB against no block were also demonstrated for pain scores at specific time points up to 24 hours post-op, parental satisfaction, and incidence of PONV.

Commentary

The erector spinae plane block, first described in 2016, has seen a rapid adoption in adult practice, where the literature supports its analgesic efficacy in a range of thoracic and abdominal surgeries. In addition, compared with conventional neuraxial blockade, it is a regional technique that is technically easier to perform and with a lower risk of major adverse events. However, the evidence for its use in the paediatric surgical population remains sparse, and so studies such as this one interrogating the utility of this block in children are useful.

There are several limitations apparent in this study. Firstly, there is no quantification of the degree of reduction in cumulative opioid consumption; instead the standardised mean difference (SMD) is used. The authors report that this was due to heterogeneity in how included studies reported opioid consumption. Without absolute values, it remains unclear whether the opioid-sparing effect is large enough to be clinically meaningful or merely statistically significant. This also applies to the authors' findings related to pain scores.

A second limitation is that there is limited data analysed relating to safety outcomes relevant to ESPB. While the authors investigated PONV, itch, and hypotension, they do not discuss more serious complications that could influence the risk-benefit assessment of ESPB in paediatrics, for example infection, haematoma, pneumothorax, and local anaesthetic toxicity.

Thirdly, there are a range of other established regional anaesthetic techniques that can be performed for the paediatric surgical procedures included in this study, such as caudal or thoracic epidural analgesia. Indeed, the authors report that when subgroup analyses were performed comparing ESPB to other blocks, then all of the statistical differences were no longer apparent, or in the case of time to first analgesic request actually favoured the group receiving other blocks. This suggests that ESPB may not offer a distinct advantage over other well-established techniques in paediatric anaesthesia, and further direct comparative trials are warranted.

Overall, whilst this meta-analysis suggests that ESPB is a promising alternative for paediatric patients undergoing trunk and hip surgery, it does not yet provide sufficient evidence to justify routine adoption over established techniques. Future studies should first focus on quantifying the clinical impact and safety profile more comprehensively, as well as determining whether ESPB is superior to existing regional techniques.

Reviewed by Dr Matt Hart

Optimizing pediatric tonsillectomy outcomes with an opioid sparing anesthesia protocol

Learning and continuously improving with real-world data

Chiem JL, Franz AM, Hansen EE, Verma ST, Stanzione TF, Bezzo LK, Richards MJ, Parikh SR, Dahl JP, Low DK, Martin LD. Optimizing pediatric tonsillectomy outcomes with an opioid sparing anesthesia protocol: Learning and continuously improving with real-world data. Paediatr Anaesth. 2024 Nov;34(11):1087-1094. doi: 10.1111/pan.14979. Epub 2024 Aug 30. PMID: 39212292.

This paper is a perspective piece primarily providing insight into how one ambulatory surgical centre utilised quality improvement processes supported by new generation artificial intelligence (AI) driven software to guide change in practice.

This describe a nine year Quality Improvement(QI) project using well established Plan-Do-Study-Act processes to foster changes from an opioid based analgesia regime for paediatric tonsillectomy to a NON-opioid based analgesic plan. This project is made possible through the data acquisition, organisation and computation software they describe.

There are 3 components of diminishing interest in this project. The most interesting feature is the use of a commercial product, AdaptX, that the company describes as artificial intelligence driven to link to Electronic Medical Records (EMR) and extract data “real time”. More importantly, it processes this data and presents it for real time assessment and interpretation. Here they present “process control charts”. Two authors declare their conflict of interest as Medical Officers of AdaptX. At least 2 subparts of this article relating to QI cycles of Opioid free anaesthesia development and Enhanced recovery have been published before ([Franz et al, 2019] and [Franz et al, 2021]).

The second is the systematic QI structure seemingly embedded in this ambulatory surgical centre that allows the development and use of multiple protocols covering multiple areas of interest as well as achieving conformity from nursing, anaesthetic and surgical staff. This project made sixteen changes to their protocols (Perioperative management x 9, Discharge opioid prescription x 3 and Enhanced Recovery x 4) over nine years.

The least compelling component is their change to opioid free techniques for day-stay tonsillectomy. This has been better covered in an earlier publication([Franz et al, 2019]). The title uses the word optimising in the context of taking a new technique (opioid free analgesia for tonsillectomy) and showing a deterioration in maximum pain score in recovery and increase in PACU opioid requirements and increased time in PACU compared to their previous opioid based intraoperative analgesia regime before instituting changes over 4 years to return to similar pain scores.

The strength of this paper is that it provides an example of a new generation of software that accesses and assesses raw EMR data to present responses to serial quality improvement protocols in real time. The increasing prevalence of electronic data availability in anaesthesia has been waiting for methods to utilise it. The question of the quality of the EMR data was not discussed in this paper and remains an evolving and potentially confounding issue. The investment by all clinical groups involved in the patients care and the real time results availability may pressure outliers to conform whether that is in improved input data accuracy or by change of clinical practice. The chosen outcome measures are easily measured but rely on data accuracy and development of the concept of what constitutes quality; these included:

- Percentage of patients receiving PACU opioid (primary measure)
- PACU pain score (secondary measure)
- Nausea and vomiting rates (secondary measure)
- Length of stay in PACU (balancing measure)

Being able to measure a variable does not assure meaningfulness. The use of programs like AdaptX will allow this discussion to occur.

The least satisfying part of the paper is the question of the place of non-opioid based analgesia for children having tonsillectomy. The authors have shown that it can be done which is of interest. This project does not convince me that avoiding opioids represents high quality anaesthesia. If their goal was to lower PACU opioid use, the reintroduction of intraoperative low dose opioid to their current regime may further decrease this. In their discussion they note some general principles regarding Obstructive Sleep Apnoea (OSA). Interestingly in the context of AdaptX, they noted that they had to manually review their departmental respiratory event database to show no change in the rate of perioperative respiratory events during this study. Hopefully it will be the next generation of Artificial Intelligence driven software that will be able to extract perioperative respiratory events amongst others from our EMRs to further our understanding of improving anaesthetic quality.

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Reviewed by Dr David Kinchington

Long-term outcomes of early exposure to repeated general anaesthesia in children with cystic fibrosis (CF-GAIN)

A multicentre, open-label, randomised controlled phase 4 trial

Wainwright CE, Vidmar S, Anderson V, Bourgeat P, Byrnes C, Carlin JB, Cheney J, Cooper P, Davidson A, Gailer N, Grayson-Collins J, Quittner A, Robertson C, Salvado O, Zannino D, Armstrong FD; ACFBAL; CF-GAIN Study Groups. Long-term outcomes of early exposure to repeated general anaesthesia in children with cystic fibrosis (CF-GAIN): a multicentre, open-label, randomised controlled phase 4 trial. Lancet Respir Med. 2024 Sep;12(9):703-713. doi: 10.1016/S2213-2600(24)00170-X. Epub 2024 Jun 5. PMID: 38851197.

Summary

Study Type:
The initial trial was a prospective, open-label, unblinded, randomised and multi-centre trial designed to look at the entirely different clinical question of pulmonary and nutritional outcomes. This study is an opportunistic 'extension study' that takes advantage of two prospectively gathered cohorts from the initial trial to serendipitously address one of the currently most pressing questions in paediatric anaesthesia: if a single, short general anaesthetic in the infant population demonstrates no significant differences in neurocognitive outcomes (as per the robust GAS trial), then do repeated and/or cumulative exposures to GAs in the under-two age group pose a cause for concern?

Methods:
This (CF-GAIN) is an opportunistic post-hoc analysis of data generated in the ACFBAL trial, which was powered to detect differences in pulmonary and nutritional outcomes at 5 years in patients with congenitally-identified cystic fibrosis who were randomised to either broncho-alveolar lavage (BAL) directed therapy or standard care. Importantly (for the question of confounders in the CF-GAIN study) there were no significant differences between these groups.

This initial trial generated two comparable cohorts, one of whom had reliably received repeated short general anaesthetics by two years of age (52 patients), and the other of whom had not (45 patients).

Exclusions criteria included:
- general anaesthesia prior to ACFBAL randomisation
- delivery via GA-C-Section
- underlying genetic conditions associated with neurocognitive issues.
Confounders such as parental educational attainment, socio-economic disadvantage, and school delay were also examined.

The initial methodology underwent a change of protocol: the extensive battery of testing was deemed too significant a burden on patients and family, so validated but shorter testing panels

were used (NEPSY-II, CPT-II, and WIS 4th ed), along with MRI brain (standardised scanning protocol). A subjective quality of life score specific to CF patients was also included. Psychologists were given a manual on the testing protocol, and families asked to not discuss which branch of the ACFBAL study they had been in.

For examination of any potential dose effect, GAs from the end of the ACFBAL up to 6 years of age were assessed.

Findings:
1. At the end of the ACFBAL trial, all of the BAL-therapy group had had multiple exposures (median 6, IQR 4-9.5); 64% (29/45) had median 2 (IQR 1-4) exposures.

2. The cumulative exposure in the first two years in the BAL group was 36 min (IQR 26-84), and in the standard care group 0min (IQR 0-0).

3. The cumulative exposure at the end of the trial (five years old) was 180 min (IQR 140-285) and standard group 48 min (IQR 30-122)

4. There were no differences between the two groups of any neurocognitive or behavioural outcomes.

5. There was no indication of a cumulative effect of GA on neurocognitive or behavioural outcomes

- a. 16% (8/49) in the BAL-group vs 2% (1/45) in the standard treatment had been held back a year in school.

- b. HOWEVER subgroup analysis found those held back were the same age as their school group peers rather than being older, suggesting maturity rather than impairment as an aetiology.

6. MRI findings – there was 'no convincing evidence of structural differences on MRI between those receiving early GA exposures and those in standard-care group. The authors note that average grey matter volume was slightly lower in the GA group and body of the corpus collosum was slightly higher, but the study was underpowered to exclude these changes occurring by chance.

Take Home Messages

Limitations:
1. This trial was done in children with CF, by definition an underlying medical condition with potential for significant impact on those affected.

2. 42% of the original ACFBAL group were lost to follow-up. However, an analysis of summary characteristics of the populations show no significant differences.

3. Data relating to cumulative general anaesthesia time was not prospectively collected, and so was reliant on retrospective collection.

4. The ACFBAL trial protocol used sevoflurane, but other agents were used. In 24 of 812 GAs, the agent(s) used were not recorded. It is unclear what, if any, impact the choice of agent may have. Cumulative exposure time was able to be assessed in 630 (78%) of GAs.

5. The study was designed to assess different outcomes; a priori powering for subtle neurocognitive changes is unclear.

Applicability:
While this study is of a population with a known pre-existing illness that may limit its generalisability to 'well' children, a lot of patients in whom early, cumulative exposure to GAs is required by the nature of their illnesses raises concerns about their potential vulnerability makes it an attractive study group.

Pending Questions:
This study, while encouraging, is hampered by the retrospective nature of its data collection and lack of a priori power design. We await the outcomes of the T-REX trial to further elucidate this question.

Reviewed by Dr Nicole Wylie

Edited by Dr Su May Koh