Total intravenous versus volatile anesthesia in pediatric cardiac surgery: inflammatory response and early recovery profiles.

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What is already known:

1. **Adult Anesthetic Comparison:** In adults undergoing coronary artery bypass grafting (CABG) surgery, propofol-based total intravenous anesthesia (TIVA) has been associated with earlier postoperative neurocognitive recovery and shorter durations of mechanical ventilation compared with volatile anesthesia, despite minimal differences in systemic inflammatory markers such as interleukin-6 (IL-6).[1]

2. **CPB-Induced Systemic Inflammation:** Cardiac surgery requiring cardiopulmonary bypass (CPB) activates a robust systemic inflammatory response syndrome (SIRS), characterized by the release of proinflammatory cytokines such as IL-6, which play a central role in clinical outcomes across pediatric and adult populations.[2]

3. **Vulnerability of Pediatric Cohorts:** In pediatric patients, this cytokine surge has heightened clinical relevance due age-related differences in immune regulation and neurodevelopmental vulnerability, which may increase susceptibility to inflammatory injury and neurocognitive sequelae after CPB.

4. **Anesthetic Immunomodulation:** The extent to which different anesthetic agents modulate this inflammatory response remains an area of ongoing investigation. Propofol-based TIVA has demonstrated potential anti-inflammatory effects, including the attenuation of IL-6 expression, whereas volatile anesthetics such as sevoflurane exhibit mixed immunomodulatory effects that vary by exposure timing, tissue environment, and surgical factors.

What this study adds:

1. **Pediatric Clinical Evidence:** This small, single-center, prospective randomized controlled trial provides valuable pediatric clinical data directly comparing propofol-based TIVA with sevoflurane-based volatile anesthesia in children (1 to 12 years of age) undergoing elective CPB surgical repair.

2. **Inflammatory Outcomes:** The study demonstrated no significant differences in systemic IL-6 concentrations between TIVA and volatile anesthesia at 24 or 48 hours post-CPB. This may be due to multiple factors, including high-dose corticosteroid administration, the substantial inflammatory response due to CPB, or the need for a more representative inflammatory marker to demonstrate clinical difference.

3. **Early Cognitive and Ventilation Recovery Benefits:** TIVA was associated with clinically significant secondary advantages, including a significantly shorter duration of postoperative mechanical ventilation (12.4 vs. 20.0 hours) and higher pediatric-adapted Mini-Mental State Examination (MMSE) scores at 24 and 48 hours post-extubation. Although the significantly shorter ventilator time in the TIVA group is an interesting finding, this finding cannot be attributed to the anesthesia technique alone, as multiple unaccounted confounding variables may have contributed. In addition, larger studies using validated, age-appropriate neurocognitive assessments and longer-term follow-up are needed to determine whether these early differences translate into meaningful neurological outcomes.

What inflammatory markers are associated with CPB?

CPB initiates a systemic inflammatory response through exposure of circulating blood elements to the foreign extracorporeal circuit surfaces, surgical trauma, and ischemic-reperfusion injury.[2,3] Key molecular markers involved include:

- **Interleukin-6 (IL-6):** A major cytokine that acts as an early orchestrator of the acute-phase inflammatory cascade and one of the most extensively studied markers following cardiac surgery. IL-6 consistently peaks around 24 hours post-CPB and serves as a validated surrogate marker of tissue injury and systemic inflammatory burden in both adult and pediatric cardiac surgery populations.[1]

- **Interleukin-8 (IL-8):** A potent neutrophil chemoattractant that promotes endothelial activation and microvascular injury post-CPB. In pediatric cardiac surgery, elevated postoperative IL-8 predicts low cardiac output syndrome (LCOS)-related outcomes, including prolonged mechanical ventilation and increased vasoactive support requirements, supporting its role as a biomarker of postoperative morbidity.[2]

- **Other Proinflammatory Cytokines (IL-1β, TNF-α):** Early mediators of the inflammatory cascade that amplify immune activation, promote endothelial dysfunction, capillary leak, and contribution to tissue injury post-CBP, particularly within vulnerable vascular beds including the pulmonary parenchyma and cerebral microvasculature.[2]

- **Regulatory Cytokines and Acute-Phase Reactants (IL-10, CRP):** IL-10 is an anti-inflammatory cytokine produced concurrently with proinflammatory mediators to limit excessive immune activation. C-reactive protein (CRP) is a downstream marker of systemic inflammation synthesized by the liver in response to circulating IL-6, commonly used as a marker of postoperative inflammatory burden.

Summary of the Study

The authors conducted a prospective, randomized, single-center controlled trial at a tertiary academic medical center of children undergoing elective repair of either atrial septal defect (ASD), ventricular septal defect (VSD), or Tetralogy of Fallot (TOF). The study was aimed to compare systemic inflammatory responses, measured by serum IL-6, in children undergoing CPB with either TIVA, or conventional sevoflurane-based volatile anesthesia.

A total of 50 children, aged 1 to 12 years, were enrolled and randomized 1:1 to either Group P (propofol TIVA, target BIS 40–60, n=25) or Group S (sevoflurane volatile maintenance, n=25). All patients received standard

anesthetic care and preoperative methylprednisolone (30 mg/kg) prior to CPB. The primary outcome was the serum IL-6 concentration measured at baseline, 24 hours, and 48 hours postoperatively. Secondary outcomes included duration of mechanical ventilation, early postoperative cognitive recovery (assessed using a modified pediatric-adapted MMSE in children aged 4 years and older, n=17 per group), hemodynamic parameters, renal/organ function, and Intensive Care Unit (ICU) length of stay.

The study's primary hypothesis was not supported, as IL-6 concentrations demonstrated similar postoperative trajectories in both groups without significant difference in systemic cytokine response. However, secondary analyses revealed that TIVA was associated with a significant reduction in mechanical ventilation duration (12.4 vs 20.0 hours; $p = 0.045$) and improved early post-extubation MMSE scores at 24 hours (23.7 vs 15.1; $p < 0.01$) and 48 hours (26.5 vs 22.2; $p = 0.02$) among children 4 years of age and older.

Key Methodological Limitations:

1. **Inflammatory Marker Profiling:** All patients received high-dose preoperative methylprednisolone (30 mg/kg), a potent immunomodulatory agent that may have attenuated any subtle, anesthetic-specific differences in cytokine expression. Given the evolving practice regarding perioperative corticosteroid use[4] in pediatric cardiac surgery, future studies may need to account for corticosteroid exposure when evaluating anesthetic-specific inflammatory effects. Broader inflammatory profiling may further help characterize these effects, including biomarkers such as IL-8, which have been localized in tracheal aspirates or bronchoalveolar lavage (BAL). This approach is supported by a 2021 meta-analysis demonstrating greater differences between propofol and sevoflurane in local pulmonary cytokines (BAL IL-6 and IL-8) than in systemic concentrations.[3] Additionally, the study did not characterize their protocol for intraoperative and post-operative blood product administration. As the volume and storage age of transfused products significantly contribute to systemic inflammation, this introduces an additional unaccounted variable.

2. **Anesthetic Depth Imbalance:** Processed electroencephalographic (EEG) monitoring with the Bispectral Index (BIS) was used solely in the TIVA group, whereas sevoflurane was titrated using age-adjusted minimum alveolar concentration (MAC) values and clinical signs. In addition, intraoperative and postoperative opioid administration was titrated based on observer clinical assessment in both groups and not defined. This lack of standardization represents a potential confounder, as both intraoperative and post-operative opioid burden could have contributed to secondary outcomes of mechanical ventilation duration and subsequent ICU length of stay. Furthermore, BIS-guided propofol titration may have facilitated more individualized anesthetic dosing, potentially contributing to shorter ventilation times and faster emergence. Future trials could consider employing standardized EEG monitoring and standardized opioid administration protocols across both groups to ensure equivalent assessment of anesthetic depth. Additionally, although BIS is widely used in pediatric anesthesia, its interpretation remains less well validated in young children because the algorithm was developed using adult EEG data, and age-dependent maturation of cortical activity may influence processed signal interpretation.[5] As such, incorporating age-specific processed EEG parameters, such as spectral edge frequency (SEF) and density spectral array (DSA), may further improve anesthetic depth assessment in future studies.

3. **Cognitive Screening Constraints:** Early postoperative cognitive recovery was evaluated using a modified MMSE, a tool validated primarily for children 4-12 years of age.[6] Consequently, its applicability to a large proportion of of participants younger than 4 years (32%) was limited, as children in this age group often lack the language, attention, and visuomotor skills required to complete the assessment. Future trials may

consider incorporating developmentally appropriate assessments across the pediatric age spectrum, such as the Cornell Assessment of Pediatric Delirium (CAPD)[7] and the National Institute of Health (NIH) Toolbox.

4. **Surgical Heterogeneity:** Participants underwent elective repair of VSD, ASD, and TOF, procedures with substantial variability in operative complexity and CPB requirements that can significantly influence the systemic inflammatory response and duration of mechanical ventilation. Randomization was not stratified by surgical complexity, and therefore differences in lesion distribution may have influenced postoperative recovery independent of anesthetic technique. Future studies could consider stratifying patients using established congenital cardiac surgical risk classifications, such as the Risk Adjustment for Congenital Heart Surgery (RACHS01) or the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality categories, to improve comparability between groups.

Take Home Points:

1. In pediatric patients undergoing cardiac surgery with CPB, propofol-based TIVA does not significantly alter postoperative systemic inflammatory responses, as measured by serum IL-6 concentrations, compared to sevoflurane-based volatile anesthesia.

2. TIVA demonstrates promising exploratory secondary benefits, including earlier postoperative cognitive recovery and shorter duration of mechanical ventilation, indicating potential advantages for fast-track recovery pathways.

3. Due to the small sample size and several important methodological limitations, including universal corticosteroid administration and unequal depth-of-anesthesia monitoring, these findings are considered exploratory. Larger, multicenter trials incorporating standardized monitoring and comprehensive, age-appropriate neurocognitive assessments are needed before definitive conclusions can be established.

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