Propofol and Survival in the Critically Ill

Key Article

- *Kotani Y., Pruna A., Turi S. et al. Propofol and survival: an updated meta-analysis of randomized clinical trials. Crit Care. 2023; 27:139.*

Background

- Propofol is commonly used for rapid sequence intubation as well as sedation in the perioperative, ICU, and ED settings. It is also commonly used for procedural sedation.
- Propofol acts on GABA receptors exhibiting CV effects via vasodilatory mechanism and CNS depression.
- Its appeal is its rapid onset and elimination.
- Acute effects of propofol as an induction agent include hypotension, respiratory depression and apnea particularly with procedural sedation.
- Proposed mechanisms of harm with propofol:
    - Propofol infusion syndrome (PRIS): characterized by metabolic acidosis, rhabdomyolysis, HLD, hepatomegaly associated with high doses and long term use
    - Accidental microbial contamination with lipophilic nature supporting bacterial growth
    - Inhibition of organ-protective effects of drugs i.e. volatile anesthetics and techniques i.e. remote ischemic preconditioning
    - HD instability and reduced myocardial contractility
- Current data
    - Avoided in pediatric population, given RCT found increased mortality among critically ill pediatric patients receiving propofol for sedation

Objective

- Investigate if there is a mortality difference between propofol and other sedative agents in postoperative and critically ill patients.

Methods

- Study/location: Meta-analysis of RCTs
- Studies
    - Included: RCTs comparing propofol to any comparator in any clinical setting
    - Excluded: RCTs with non-parallel design (cross over), overlapping publications, non-human studies, propofol used for palliative or end of life care, propofol used as single IV bolus or for minor procedures
- Trial procedures
    - Two investigators searched PubMed, Google Scholar, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov up to August 19th, 2022.
    - Assessed risk of bias using Cochrane risk of bias tool for randomized trials
    - Standardized data collection form used. RR and NNH calculated.

    - Subgroup analysis performed to evaluate differences in clinical settings, surgical vs non-surgical patients, and use of propofol in comparator arm.
- Primary outcome
    - All-cause mortality at the longest follow up available

Results

- 11,204 records identified
    - 252 RCTs included (30,757 patients between 1987-2022)
        - Setting
            - 200 surgical: 153 non-cardiac surgery; 47 cardiac surgery
            - 52 ICU
        - Comparator
            - 172 volatile anesthetics
            - 71 IV agents
- Primary Outcomes – All-Cause Mortality
    - Overall population
        - Propofol group: 5.2%
        - Comparator group: 4.3%
        - RR 1.1, 95% CI 1.01-1.2; p = 0.03
        - NNH 235
        - Statistically significant
    - Subgroup: ICU vs cardiac vs non-cardiac surgery
        - Only statistically significant for cardiac surgery
        - For ICU
            - Propofol: 15%
            - Comparator group: 13%
            - RR 1.04, 95% CI 0.93-1.16; p = 0.5
            - NOT statistically significant
    - Remaining subgroups analysis “magnitude and direction” maintained

Limitations Identified by Authors

- High risk of bias in 16% of studies. Noted mortality difference when excluded biased studies.
- Unable to double blind studies given close titration of medications in periop and ICU settings
- Mortality outcome time point varied with studies. Used mortality at longest follow up.
- Potential confounder being duration of infusion (data was not available)
- Likely sedative cross over. Other potentially detrimental hypnotic agents likely used in propofol group as well confounding relationship between propofol and mortality
- Limited generalizability since majority of studies were volatile anesthetics likely perioperative setting.

Take Home Points

- Propofol increased mortality in this study by 10% compared to other hypnotic agents. However, no statistically significant mortality increase when ICU subgroup analysis performed.
- In addition to the hypnotic agent possibly having a difference in outcomes, the depth and duration of sedation likely has implications as well. Important to prioritize lighter sedation and sedation holidays for critically ill patients.