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INHALATION VERSUS TOTAL INTRAVENOUS ANESTHESIA: A LITERATURE REVIEW

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Abstract: Postoperative delirium, an acute condition characterized by reduced awareness of the environment and disturbance in attention, usually occurs between 24 and 72 hours after surgery and can affect up to 60% of elderly surgical patients. Postoperative cognitive dysfunction (POCD) is a new onset of cognitive impairment that may persist for weeks or months after surgery. The primary objective of this study was to review the literature on the clinical impact of the choice of general anesthesia on the incidence of POCD, whether inhaled or total intravenous anesthesia in the first 30 days, excluding assessments on the same day of surgery. In conclusion, total intravenous anesthesia may be associated with a lower incidence of POCD, compared to inhalational anesthesia, at least in the first 30 postoperative days. However, future studies investigating POCD must focus on assessments of attention because the validity of testing all other cognitive subdomains (for example: memory, executive functions) depends on their integrity. This could also reduce heterogeneity in POCD research.
Keywords: Inhalation anesthesia; total intravenous anesthesia; anesthesiology.

INTRODUCTION

Inhalation anesthesia as well as total intravenous anesthesia (TIVA) have been used worldwide for decades in the maintenance of anesthesia. However, there is no consensus on perioperative management, which may affect the final result. The present study aimed to assess the difference between the TIVA and inhalation groups and determine the impact of anesthetic management on postoperative complications.

When maintenance of general anesthesia is by intravenous (IV) infusion, this is referred to as TIVA. Although TIVA has advantages for some patients and is the technique of

choice for some anesthesiologists, the most common technique used for maintenance of anesthesia in the UK and Ireland remains the administration of an inhaled volatile anesthetic. However, the use of an inhalation technique is sometimes not possible, for example anesthesia administered outside the operating room, during transfer or for some airway operations. In addition, in some situations inhalation anesthesia is contraindicated, for example in patients with malignant hyperthermia, or TIVA may be advantageous, for example in patients at high risk of postoperative nausea and vomiting (PONV) or when it is necessary intraoperative monitoring of somatosensory or motor evoked potentials. Therefore, all anesthesiologists must be able to administer TIVA competently and safely.

The knowledge required by an anesthesiologist using TIVA includes: the principles behind achieving and maintaining an adequate plasma and brain concentration of the intravenous anesthetic drug; the factors that determine the appropriate target drug concentration and how to adjust it in light of the patient's response; practical aspects involved in ensuring that the intended dose of medication is delivered to the patient; monitoring the patient receiving TIVA, including the use and interpretation of pEEG monitors.

In focus, postoperative cognitive dysfunction (POCD) is a common condition after surgery and anesthesia (GLUMAC et al. 2019; BALLARD et al. 2012). Recent studies have shown an incidence of POCD between 10%-18% (KONISHI et al. 2018). The International Study of Post-Operative Cognitive Dysfunction (ISPOCD-1) estimated that the incidence of POCD after non-cardiac surgery reaches 9.9% at three months (MOLLER et al).

Regarding the choice of type of general anesthesia, previous studies have identified a possible role of propofol in the attenuation of the inflammatory cascade (CHEN et al. 2005). Furthermore, an increase in several cytokines, including IL-6, TNF-α, IL-8, and IL-10, was associated with the presence of POCD (SKVARC et al. 2018). Consequently, TIVA can be hypothesized to be protective against POCD.

A consensus working group published recommendations from an expert panel suggesting that cognitive assessments in POCD must be differentiated into delayed cognitive recovery (DCR), for example: assessments up to 30 days postoperatively, and postoperative neurocognitive disorder (pNCD), that is, assessments performed between 30 days and 12 months after surgery. The consensus working group emphasized that cognitive decline after the first 30 days postoperatively could potentially be linked to long-term consequences and therefore must also be a topic of research. (EVERED et al. 2018).

The primary objective of this study was to review the literature on the clinical impact of the choice of general anesthesia on the incidence of POCD - DCR, whether inhaled or total intravenous anesthesia (TIVA) in the first 30 days, excluding assessments on the same day of surgery. As a secondary objective, we performed a literature review to study the impact of anesthetic choice on the incidence of POCD - pNCD between 30 days and 12 months postoperatively.

Anti-inflammatory effects may also contribute to propofol-related cardioprotection (CRUZ et al. 2021). Furthermore, a previous RCT reported that, compared to AV, TIVA could control stress and hemodynamic response in patients undergoing coronary artery bypass graft surgery, contributing to a cardioprotective effect (ONK et al. 2016).

Interestingly, the combination of the effects of isoflurane preconditioning and propofol postconditioning resulted in a postoperative decrease in MB isoenzyme releasing CK and cTn I and facilitated postoperative myocardial functional recovery compared to the anesthetized control group. with fentanyl and midazolam, suggesting a potential synergism in the modulation of IR injury after CPB (HUANG et al. 2011).

MATERIAL AND METHODS

A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); base; Web of Science, Google Scholar. Conference abstracts/articles have been deleted from Embase. No other limits have been applied. All retrieved records were organized using the Endnote citation management software version 20. For the removal of duplicates, a review software and literature review citation screening software were used.

The search strategy was designed to capture the association between postoperative cognitive dysfunction (POCD) with surgical anesthetics, specifically propofol and inhalational agents. The searches were complemented by manual searching and retrieval of any additional articles that met the eligibility criteria that were cited in our reference lists.

RESULTS

In the article by Chang et al. 2016, 96 patients in the TIVA group were compared with 87 patients who received inhalation anesthesia. There were no differences in gender, age, physical status classification based on the American Society for Anesthesiologists (ASA) score, and comorbidities between the two groups. Patients in the TIVA group required less perioperative crystalloid and colloid to maintain hemodynamic stability. Although the mean duration of anesthesia was shorter in the TIVA group (11.02 ± 2.84 vs. 11.70 ± 1.96 hours, $p = 0.017$), blood loss was similar between the groups ($p = 0.71$). There was no difference in the rate of surgical complications, but patients in the TIVA group developed fewer pulmonary complications (18 vs. 47, $p = 0.0008$). After multivariate regression, patients in the TIVA group had a significantly reduced risk of pulmonary complications compared to the inhalation group. Total intravenous anesthesia was associated with significantly fewer pulmonary complications in patients who received free flap reconstruction.

DISCUSSION

The results of our review suggested that the incidence of POCD - DCR after the use of TIVA may be lower compared to inhalation anesthesia in the first 30 postoperative days. Our study suggests that the concept of POCD must be redefined to a more objective definition. In addition, it would be interesting to assess a more basic cognitive domain, such as attention, in all awake and alert individuals, as it is well known in the literature that attention plays a central role in the functions of all other cognitive domains. It is reasonable to assume that specific cognitive deficits, such as memory, executive function, among others, may reflect an underlying attention deficit. Future research must focus on objective measures of attention before other specific cognitive domains. This would allow for a reduction in heterogeneity in POCD research.

The potential benefits of propofol and TIVA in POCD may be mediated by their positive effects in decreasing the inflammatory cascade. Evidence has shown that propofol has anti-inflammatory properties compared to inhaled agents (LEE et al. 2010) as results from in vivo studies have shown lower levels of circulating cytokines and other mediators

of inflammation in animals injected with propofol (SKVARC et al.. 2012). Inflammation has been linked to POCD in many different studies. An increase in several cytokines, including IL-6, TNF-α, IL-8 and IL-10, has been correlated with postoperative cognitive impairment. Recently, a meta-analysis was performed evaluating the association between various inflammatory biomarkers and POCD and concluded that postoperative C-reactive protein (n = 11 studies) and IL-6 (n = 17 studies) were associated with POCD (LIU et al. al. 2018). However, the possible role of anesthetics in the inflammatory cascade remains unclear, with some evidence favoring the use of inhalational agents such as sevoflurane specifically in cellular models of ischemia-reperfusion (LI et al 2020).

A limitation that must be highlighted refers to the fact that propofol was used in both groups in all included studies, at least as a single bolus agent in the anesthesia induction phase. It is uncertain whether a single dose of propofol can exert any potential beneficial effect on POCD, hence its potential effects on the inflammatory cascade, even considering that in the TIVA group propofol is used in continuous infusion throughout the duration of the procedure. Perhaps future studies on POCD must consider the use of another induction agent in the inhalation group in the study design phase.

Only two authors in our review reported which specific tests showed a significant difference in their postoperative assessment. One study reported that the most altered tests were the Semantic Verbal Fluency and the Letter Number Sequence Test, which measures executive function and the cognitive domains of working memory, speed and visual space (KLETECKA et al. 2019). Another author reported that the COWAT, the Stroop Neuropsychological Screening, the Clock Test, the Three Word-Three Shapes, the Babcock Story Recall, the Instrumental Activities Daily Living (IADLS) and the TMT-B as tests showed a difference in their postpartum assessment. -operative (MICHA et al. 2016).

In another perspective, the systematic review of the current literature carried out by Stefan et al. 2022 reported that it is currently difficult to conclude whether one anesthetic approach is superior to another in terms of patient outcome and there is no strong recommendation on the use of a specific regimen. Whether anesthetic preconditioning actually contributes to the anti-ischemic effects of VA and these effects translate into better outcomes in cardiac surgery patients at risk of perioperative myocardial ischemia has not been definitively established. Factors such as non-uniform extent of ischemic insult, type of surgery, time of aortic clamping and type of cardioplegia, presence of comorbidities, effects of concomitant medication, different anesthesia protocols (time, dosage, type of agent) and outcome definitions may influence the results of different studies. Large RCTs, including high-risk patients, homogeneous for surgical and anesthetic protocols, are needed to assess the impact of anesthetics (STEFAN et al. 2022).

On the other hand, IR injury in cardiac surgery is too complex to be the target of a single intervention, such as the choice of anesthetic regimen. Most likely, the perioperative outcome of cardiac surgery patients depends more on how anesthesiologists use available tools, anesthetic agents, adjuvants and vasoactive drugs to control the homeostasis of these patients and manage temperature, hemoglobin levels, hemostasis, cardiovascular changes, glycemic control, protective ventilation and other factors that can also affect the result. The selection of the anesthetic regimen must also consider the

technical and pharmacokinetic challenges focused on the demands of each patient. The skill and dedication of the anesthesiologist is probably much more important than which medications are being used (STEFAN et al. 2022).

The most important finding in the study by Cheng et al. 2016 was that patients in the TIVA group had a significant association with fewer postoperative pulmonary complications (18 vs.47, $p < 0.0008$). Indeed, it is reasonable to speculate that because of the significantly lower perioperative fluid requirement in the TIVA group, fewer postoperative pulmonary complications developed. Several studies have suggested that repeated fluid resuscitation could lead to increased postoperative medical complications (Haughey et al. 2001; Clark et al. 2007). The finding is in agreement with that of a study by Zhong et al. which showed crystalloid was an independent risk factor for postoperative complications and suggested that the crystalloid volume replacement rate must be between 3.5 and 6 ml/kg/h. The difference in overall fluid balance can also lead to fewer pulmonary complications. In this study, the overall fluid balance in the TIVA group (2316.30 ± 1056.73 ml) was significantly lower than in the inhalation group, which was similar to the results of a recently published national survey in the United Kingdom (GOONERATNE et al. 2013).

Propofol plays a central role in total intravenous anesthesia (TIVA). In addition to its ability to maintain vascular resistance, propofol has been suggested to modulate the inflammatory response (WEI et al. 2013) and attenuate endotoxin-induced endothelial cell injury (VOTTA-VELIS et al. 2007) during acute lung injury.. Therefore, for patients whose lung compliance has deteriorated due to general anesthesia and prolonged ventilatory support, propofol is considered a protective effect against postoperative pulmonary complications by reducing the systemic inflammatory response. The use of inhaled and intravenous anesthetics in ischemia-reperfusion injury (KATO et al. 2002), ischemic preconditioning or inflammatory response of the lungs (NG et al. 2011) remains controversial.

Some investigators may be concerned about the possibility of metabolic acidosis after prolonged infusion of propofol, such as propofol infusion syndrome (SIRS), which would cause damage to a fresh anastomotic flap and enlargement. Although there is an association between PRIS and propofol infusion at doses higher than 4 mg.kg -1.h -1 when the time of use is longer than 48 h (KAM et al. 2007), the target concentration at the site of effect of the present study was 3.0~ 5.0mcg·ml -1 and the mean duration of anesthesia was only 11.40± 2.40 hours. In this study, there was no difference in the rate of surgical complications between the two groups. TIVA has been applied in many types of surgery without the development of PRIS (GRUPTA et al. 2004). The main limitations of this study were its retrospective design and small sample size. As this is a retrospective analysis, no causality can be inferred from our results. Future prospective controlled studies are needed to clarify the beneficial effect and causal associations of different types of anesthesia. In conclusion, patients who received TIVA had a lower need for fluids during free flap surgery; thus, pulmonary complications were reduced by almost 60%. Anesthetics such as propofol may be able to reduce the occurrence of pulmonary complications with no significant difference in surgical complication in free flap surgery for head and neck cancer.

FINAL CONSIDERATIONS

In conclusion, TIVA may be associated with a lower incidence of POCD, compared to inhalation anesthesia, at least in the first 30 postoperative days. However, future studies investigating POCD must focus on attentional assessments because the validity of testing all other cognitive subdomains (for example: memory, executive functions, etc.) depends on their integrity. This could also reduce heterogeneity in POCD research.

We are uncertain whether maintenance with propofol-based TIVA or with inhalational agents affects the incidence of postoperative delirium, mortality, or length of hospital stay because the certainty of the evidence was very low. We found low certainty evidence that propofol-based TIVA maintenance can reduce POCD. It was not possible to perform a meta-analysis for intraoperative hypotension or length of stay in the PACU due to heterogeneity between studies. We identified 11 ongoing studies from searches of clinical trial registries; including these studies in future review updates may provide more certainty for the review results.

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