



Review Article

Korean J Anesthesiol 2022;75(5):363-370
<https://doi.org/10.4097/kja.22517>
pISSN 2005-6419 • eISSN 2005-7563

Received: August 13, 2022
Revised: August 22, 2022
Accepted: September 18, 2022

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Total intravenous anesthesia for liver resections: anesthetic implications and safety

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Inhalational anesthetics have been the default agents for general anesthesia maintenance for several decades. However, with advances in total intravenous anesthesia (TIVA) and a growing body of evidence on the potential benefits of TIVA, anesthesiologists need to question this paradigm. Some of the benefits of propofol-based TIVA, such as its antiemetic properties and patients' smooth emergence, are widely acknowledged. A growing body of evidence suggests that TIVA may potentially benefit the immune system and cancer outcomes. From an existential health perspective, there is evidence that inhalational agents have a materially higher global warming potential than propofol-based TIVA. Despite the compelling potential benefits of propofol-based TIVA, there are barriers to its widespread adoption. To examine the applicability of TIVA as a mainstay agent more rigorously, we discuss the safety and applicability of propofol-based TIVA in the context of complex major abdominal surgery, specifically, liver resection surgery. We also discuss the use of propofol-based TIVA in liver resection surgery with a broad, integrated approach, addressing general and specific clinical considerations, economic factors, and operating room turnover.

Keywords: Desflurane; Hepatectomy; Inhalational anesthetics; Intravenous anesthetics; Sevoflurane; Volatile.

Introduction

Anesthesiologists are key players in advocating for patient safety and outcomes, as their actions can have immediate and long-term repercussions for patients [1,2]. The role of anesthesiologists is to provide optimal conditions for surgery, ameliorate the surgical stress response, prevent organ injury, and achieve quality postoperative analgesia [3-5]. In recent decades, volatile anesthetics have been the mainstay of our practice. However, a growing body of evidence suggests that total intravenous anesthesia (TIVA) may have benefits over inhalational anesthetics in terms of cancer outcomes, postoperative pain scores, and the surgical stress response [6]. Another supplementary benefit of TIVA is the much lower greenhouse gas impact of propofol compared to inhalational anesthetics; an impact that is four orders of magnitude lower than that of desflurane and nitrous oxide [7]. The theoretical advantages and disadvantages of TIVA over inhalational anesthetics in the general context have been clearly shown [8]. However, we have less certainty with regard to the pragmatic applications of TIVA in complex surgeries such as hepatic resection. The purpose of our narrative review is thus to examine the feasibility and safety of TIVA in a specific clinical context, such as anesthesia for hepatic resection. We aim to weigh the advantages and potential disadvantages of using TIVA in complex surgeries such as hepatic resection ma-

for abdominal surgery with complicated perioperative management.

Potential advantages of TIVA for hepatic resection

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of general anesthesia, with an incidence of 30–80% [9]. In the context of major abdominal surgery, careful attention should be paid to adequate PONV prophylaxis [10]. A multimodal approach within an enhanced recovery after surgery pathway allows the majority of patients to resume feeding on postoperative day 1 [11]. One of the recommended strategies for reducing the baseline risk of PONV is the preferential use of TIVA and avoidance of nitrous oxide and volatile anesthetics [12]. By conservative estimates, a patient presenting for hepatic resection will have at least four known risk factors for PONV: general anesthesia, postoperative opioids, long duration of anesthesia, and intra-abdominal surgery [12]. The use of volatile anesthetics for maintenance presents an additional risk factor. Consensus guidelines now recommend two modes of prophylaxis for patients with 1–2 risk factors and 3–4 modes of prophylaxis for patients with more than two risk factors [12]. In 2018, a meta-analysis demonstrated that TIVA reduces the relative risk of PONV by 39% (95% CI [31%, 47%]) compared with volatile anesthetics [13].

Postoperative delirium and confusion

Hepatic resection is a complex surgery that may be associated with a 20–50% risk of postoperative delirium [14]. Risk factors include advanced age, reduced serum albumin concentrations, cerebrovascular disorders, cardiovascular diseases, diabetes mellitus, benzodiazepine use, and a previous history of delirium [15]. Postoperative cognitive dysfunction (POCD) is characterized by acute and fluctuating impairments in attention and awareness. It is a serious complication that increases the length of hospital stay by 2–3 days and is associated with a 30-day mortality of 7–10% [14]. In a multicenter randomized controlled trial designed to study the incidence of postoperative delirium in two groups of patients assigned to light or deep anesthesia guided by bispectral index (BIS) monitoring, targeting light anesthesia was found to reduce the risk of POCD at 1 year (9% vs. 20% reduction based on an Abbreviated Mental Test score ≤ 6 , $P < 0.001$) [16]. To date, however, studies have been equivocal, resulting in a lack of convincing evidence of any difference in the incidence of POCD between propo-

fol-TIVA and inhalational anesthesia [17–21]. Nevertheless, current guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia recommend the use of processed electroencephalogram (pEEG) monitoring when a neuromuscular blocking drug is used with TIVA [22], which may be beneficial for avoiding excessive anesthetic depth. Intraoperative neuromonitoring is associated with a lower risk of delirium; however, the mechanism for this association is unknown and more studies are therefore needed [23,24].

Postoperative pain

In animal studies, propofol has been shown to decrease inflammatory cytokine concentrations and prevent the activation of N-methyl-D-aspartate receptors [25,26]. Some clinical studies have also suggested that propofol TIVA is associated with a reduction in postoperative pain [27,28]. A subgroup analysis in a recent retrospective cohort study found that propofol TIVA was associated with a clinically significant reduction in postoperative pain scores and opioid consumption in patients undergoing hepatobiliary and pancreatic surgery [29]. Another retrospective study found that propofol TIVA was associated with less pain during coughing and reduced morphine consumption in patients undergoing liver surgery [30]. Additionally, a scoping review of 16 clinical trials in 2020 compared the effects of propofol TIVA against inhalational anesthetics on postoperative pain scores and/or opioid consumption. The authors found that propofol TIVA had comparative benefits in nine clinical trials, resulted in worse outcomes in two clinical trials, and was no different from inhalational anesthetics in five clinical trials [31]. A meta-analysis reviewing the differences in postoperative analgesia between propofol TIVA and inhaled general anesthesia maintenance that was conducted before the aforementioned review found that propofol TIVA was associated with a statistically significant but minimal reduction in pain scores at 24 h [32].

Ischemic-reperfusion injury

Hemorrhage during liver resection is a significant threat to good clinical outcomes. However, while portal triad occlusion with complete clamping of the hepatic inflow is a useful means of minimizing intraoperative blood loss, ischemia and subsequent reperfusion injury of the liver is a primary concern [33]. Ischemic-reperfusion injury during liver resection involves Kupffer cells releasing reactive oxygen species (ROS) and proinflammatory mediators, which in turn leads to oxidative damage, induction of p53, apoptosis, and necrosis of hepatocytes and endothelial

cells [34]. Propofol is known to possess free radical-scavenging properties, as demonstrated by both in vivo and in vitro studies. This occurs either through direct chelation of ROS by propofol-derived phenoxy radicals or by increasing the antioxidant defense capacity [35,36]. Propofol has also been shown to protect against hepatic ischemia-reperfusion injury by inhibiting B-cell leukemia/ lymphoma 2 (BCL-2)/adenovirus E1B interacting protein 3 (BNIP3)-mediated oxidative stress [37]. One study that compared propofol infusion with isoflurane anesthesia during one-lung ventilation found that ROS production occurred to a lesser extent in the propofol group. The choice of anesthetic agent may alter the balance between antioxidant and oxidant concentrations. The total antioxidant status increased with time in the propofol group but not in the isoflurane group [38].

Acute kidney injury

Acute kidney injury (AKI) occurs in approximately 15% of patients undergoing liver resection surgery and is a potential cause of postoperative morbidity and mortality [39–41]. While many factors may contribute to the development of AKI, it is most frequently caused by acute tubular necrosis secondary to perioperative hypovolemia and hypotension. A recent single-center parallel randomized control study assessing perioperative renal function in patients anesthetized with either TIVA or sevoflurane found that sevoflurane anesthesia reduced urine output and sodium excretion and increased plasma renin concentrations compared with TIVA anesthesia [42]. The Volatile Anesthetic Protection Of Renal Transplants-1 (VAPOR-1) randomized controlled trial compared the impact of propofol vs. sevoflurane-based anesthesia during living donor kidney transplantation and found that while urinary biomarkers of kidney injury were increased on day 2 in the sevoflurane group, no significant differences in graft outcomes were seen. Notably, there was a lower acute rejection rate after two years in the sevoflurane group [43]. More studies, including the VAPOR-2 trial, will need to be evaluated before further conclusions can be reached.

Cancer outcomes

An observational study of 2,097 patients performed in the United States found that the most common indications for hepatic resection were secondary metastases (52%), primary hepatic malignancy (16%), biliary tract malignancy (10%), and benign hepatic tumors (5%) [44]. Given that most hepatic resections are performed for malignancies, another factor worth considering is the effect of anesthetic choice on cancer outcomes. While cancer out-

comes are influenced by multiple factors, the choice of anesthetic is directly based on the anesthesiologist's purview. A survey conducted on the practice patterns of anesthesiologists suggests that volatile-based anesthesia is a prevalent anesthetic technique in cancer surgery [45]. However, a developing body of evidence suggests that propofol-based TIVA may be linked to more favorable long-term cancer outcomes than volatile-based anesthesia [46–49]. Preclinical studies have demonstrated that volatile anesthetics affect innate and adaptive immune cell function and exert immunosuppressive effects. Mechanisms include decreased neutrophil recruitment and adhesion, reduced phagocytosis, decreased natural killer (NK) cell activity, and polarization of T lymphocytes toward a protumorigenic T helper 2 (Th2) cell population [50–52]. In comparison, propofol tends to maintain immune function and does not weaken the cytotoxic activity of NK cells [6]. Additionally, volatile anesthetics exhibit protumorigenic activity by increasing tumor growth, migration, and invasion in several types of cancers, including prostate, renal cell, ovarian, hepatocellular, and breast cancers. In contrast, propofol has been demonstrated to decrease tumor cell proliferation in breast, endometrial, prostate, lung, and gastric cancers; squamous cell carcinoma; glioblastoma; osteosarcoma; and leukemia [53]. A meta-analysis of TIVA vs. volatile anesthesia concluded that propofol TIVA may be associated with improved recurrence-free survival and overall survival in patients undergoing cancer surgery [47]. Despite evidence suggesting that TIVA may be the preferred anesthetic for patients undergoing cancer surgery, some degree of equipoise remains since the evidence currently available is derived from studies that are underpowered and/or flawed in their methodology. Currently, the Volatile Anesthesia and Perioperative Outcomes Related to Cancer trial, a large international multicenter randomized controlled trial, is in progress. Table 1 lists the studies comparing cancer outcomes in patients who received either TIVA or inhalational anesthesia for oncosurgery.

Safety and potential disadvantages of TIVA for hepatic resection

Hepatic blood flow

Hepatic resection has the potential to cause significant blood loss. Some strategies to reduce surgical blood loss include low central venous pressure (CVP), temporary inflow occlusion (Pringle maneuver), and other blood-loss-limiting surgical techniques [54]. Hence, the influence of TIVA versus inhalational anesthetic agents on hepatic blood flow should be examined. Propofol has been hypothesized to potentially increase hepatic blood flow and

Table 1. Studies Comparing Total Intravenous Anesthesia vs. Inhalational Anesthesia in terms of Cancer Outcomes

Author, year	Method	Number of patients	Main findings	Main limitations
Meng et al., 2020 [49]	Retrospective, cohort study	1,513	Patients receiving inhalational anesthesia have a lower 5-year overall survival rate than patients receiving TIVA [12.6% (95% CI, 9.0, 17.3) vs. 17.7% (95% CI, 11.3, 20.8), $P = 0.024$]	Not randomized, prospective study
Yap et al., 2019 [47]	Meta-analysis	7,866	Propofol-TIVA use may be associated with improved recurrence-free survival and overall survival in patients undergoing surgery	Inherent limitations of studies included in the meta-analysis
Yan et al., 2018 [48]	Prospective, randomized controlled study	50	In comparison with sevoflurane-based inhalational anesthesia, propofol/remifentanyl-based TIVA can effectively inhibit the release of VEGF-C induced by breast surgery but did not seem to be beneficial in the short-term recurrence rate of breast cancer	Study may be underpowered
Wigmore et al., 2016 [46]	Retrospective, propensity-matched analysis	5,214	Volatile inhalational anesthesia was associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis of known confounders in the matched group	Not randomized, prospective study

TIVA: total intravenous anesthesia.

alter hepatic oxygen consumption. A small animal study using a rabbit model compared the effects of intralipid and propofol infusions on hepatic blood flow and hepatic oxygenation and concluded that propofol increases total hepatic blood flow via increased hepatic portal venous flow and hepatic oxygen consumption; however, the hepatic oxygen balance was found to be preserved in this study [55]. A small crossover study was also performed in patients aged ≥ 18 years who were scheduled for general anesthesia ($n = 20$) in which patients were randomized to receive either propofol or desflurane under general anesthesia. Propofol was associated with notably higher blood flow in the right and middle hepatic veins than desflurane, as assessed by transesophageal echocardiography. However, this study had significant limitations, as neither baseline hepatic blood flow, total hepatic blood flow, nor hepatic oxygen consumption were directly measured. Additionally, the clinical implications of the findings regarding the balance between hepatic blood flow and hepatic oxygen consumption were not clear, including whether the net effects were beneficial or detrimental [56]. A more recent randomized controlled trial conducted by van Limmen et al. [57] in 2020 ($n = 18$), which compared the effects of propofol and sevoflurane on hepatic blood flow in patients undergoing pancreaticoduodenectomy, showed that hepatic blood flow was similar in both groups using a goal-directed hemodynamic therapy approach. Due to the paucity of data, however, more information is needed before conclusions can be drawn regarding the clinical effects of propofol on hepatic blood flow and metabolism in humans.

Hemodynamic effects

Propofol has significant effects on the cardiovascular system that is more pronounced in elderly and frail patients [58]. Specifically, propofol causes a dose-dependent reduction in systemic blood pressure and cardiac output, primarily through vasodilatation and cardiovascular depression [59,60]. Therefore, if cardiac output is not adequately maintained, liver and kidney perfusion can be compromised [58]. Milne et al. [61] described the use of propofol TIVA target-controlled infusion (TCI) and remifentanyl infusions to provide anesthesia for major hepatic resection. The authors reported low blood loss (ranging from 300 to 2,000 ml) and rapid patient recovery without any need for postoperative intensive care. The authors also postulated that propofol-induced vasodilatation was beneficial in reducing CVP and resulted in less venous distension in the liver, leading to reduced blood loss. More prospective randomized studies are required to investigate the hemodynamic effects of TIVA for hepatic resection.

Accidental awareness under general anesthesia

The 5th National Audit Project (NAP 5) concluded that self-reported cases of accidental awareness under general anesthesia (AAGA) were more common with TIVA; however, most cases were avoidable. The most significant contributing factor was insufficient education and training [62]. Mistakes made during the delivery of TIVA may lead to overdosing, underdosing, and AAGA. According to NAP 5, the leading causes of AAGA were

failure to administer the required dose of the drug and inadequate understanding of the underlying pharmacological principles of TIVA [22,62]. Recommendations include TCI, TIVA-specific administration sets, maintaining visibility of intravenous access whenever feasible, and pEEG monitoring when a neuromuscular blocker is used in conjunction with TIVA [22].

Turnover time

An international survey on the factors influencing the use of TIVA among anesthesiologists found that concerns about increased turnover time ranked highly on the list of reasons for not using TIVA. Of note, increased turnover time was of much lower importance amongst frequent users of TIVA when not selecting TIVA [63]. A few studies have compared the anesthetic turnover time for TIVA versus inhalational anesthesia. One retrospective study found that the time to extubation was shorter in patients receiving desflurane than in those receiving TCI-based propofol TIVA for open liver surgery [64]. Another comparison between propofol TIVA and desflurane anesthesia in patients undergoing functional endoscopic sinus surgery found that the propofol group emerged from anesthesia faster and had a lower risk of prolonged extubation time after anesthesia [65]. In two randomized clinical trials, BIS monitoring reduced propofol consumption and hastened recovery after propofol-TIVA in patients undergoing gynecological surgery [66,67]. Another randomized clinical trial comparing the effect of BIS titration in patients receiving propofol-alfentanil and nitrous oxide anesthesia concluded that titrating propofol with BIS monitoring was associated with reduced propofol administration, shorter time to extubation and improved quality of recovery [68]. Another potential consideration regarding the use of TIVA in hepatic resection is the impact of surgery on the hepatic metabolism of propofol. The liver is the predominant site for propofol metabolism. The majority of propofol (70%) is conjugated to propofol glucuronide by uridine 5'-diphosphate glucuronosyltransferase. Approximately 29% of propofol is hydroxylated to 2,6-diisopropyl-1,4-quinol (4-hydroxypropofol) [58]. Extrahepatic metabolism in the kidneys, small intestine, and lungs accounts for 40% of total propofol clearance. The liver is highly efficient in metabolizing propofol, with a blood extraction ratio of 0.9 [58]. Hence, recovery from TIVA may be delayed after hepatic resection surgery compared to non-hepatic surgery [69]. The impact of hepatic resection on total propofol clearance may be more significant for major hepatic resections, considering the duration of surgery, context-sensitive half time, and reduced propofol metabolism [70].

Cost-effectiveness

The cost-effectiveness of TIVA is another potential consideration for anesthesiologists deciding between TIVA and inhalational anesthesia [63]. While no relevant studies have been performed on TIVA for hepatic resection, a recent meta-analysis conducted in the United States compared the cost-effectiveness of TIVA versus inhalational anesthetics for non-cardiac surgery [71]. The results showed that general anesthesia maintenance with propofol TIVA was associated with a lower PONV rate, shorter stay in the post-anesthesia care unit, and reduced rescue anti-emetic requirements, negating the greater costs for anesthetics, analgesics, and neuromuscular blockers for propofol TIVA. The results were consistent in both inpatient and ambulatory surgical settings [71]. With the availability of generic propofol and open-loop TCI systems, TIVA can potentially be much cheaper than sevoflurane and desflurane, even before factoring the costs that may arise from postoperative recovery [72].

Conclusion

TIVA is a promising technique for hepatic resection. Lack of familiarity with and experience in using TIVA for hepatic resection, however, are potential barriers to its use. Other potential barriers include concerns regarding AAGA, increased operating room turnover time, and hemodynamic stability in the context of a low-CVP anesthetic technique. However, TIVA may potentially improve the patient's postoperative recovery profile, reduce PONV and postoperative opioid requirements, and have a positive impact on cancer outcomes. The learning curve associated with the use of TIVA, however, may be even steeper when applied to a complex, major abdominal procedure such as hepatic resection.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Selene Yan Ling Tan (Conceptualization; Data curation; Writing – original draft)

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