# Total Intravenous Anesthesia and Anesthetic Outcomes

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THE PROVISION of general anesthesia (GA) through intravenous agents alone is known as total intravenous anesthesia (TIVA). TIVA has become more popular in the past 20 years because of the pharmacokinetic and pharmacodynamic properties of propofol and the availability of short-acting synthetic opioids.

The use of TIVA has a number of theoretical advantages over inhalational agents to maintain GA. Drugs used for TIVA decrease the risk of side effects of GA such as postoperative nausea and vomiting (PONV) and avoid pollution of environmental air with the inhalational agents.

Despite these and other potential advantages, the use of TIVA remains low. Concerns exist about the increased possibility of patient awareness with TIVA as opposed to the use of inhalational agents with end-tidal agent concentration monitoring.

This review will explore the advantages and disadvantages of TIVA with a focus on anesthesia outcomes. The clinical issues examined will include emergence from anesthesia, PONV, ischemic preconditioning, and emerging work on postoperative acute and chronic pain.

## PROPERTIES OF AN IDEAL ANESTHETIC AGENT

There are a number of properties that can be thought of when considering the ideal anesthetic agent: rapid onset and offset; rapid emergence; rapid recovery to baseline; analgesia at subanesthetic concentrations; antiemetic effect; minimal cardiovascular and respiratory depression; absence of active metabolites; organ independent metabolism; easily titratable; no interaction with neuromuscular blocking drugs; no toxic effects on other organs; antioxidant, anti-inflammatory; long shelf life; no hypersensitivity reactions or release of histamine; safe if inadvertently injected into an artery; green (atmosphere friendly).

None of the agents currently available meets all these requirements. However, TIVA with propofol has a number of potential advantages over inhalational agents.

## RECOVERY FROM ANESTHESIA

Recovery after anesthesia and surgery is a complex process dependent on patient, surgical, and anesthetic characteristics, as well as presence of any of numerous adverse sequelae.[1]

The pharmacokinetics and pharmacodynamics of propofol-opioid combinations in TIVA have been described in increasing detail over the past 30 years. Propofol is well suited for continuous infusion techniques, because its context-sensitive half-life increases by only 20 to 30 minutes with infusion durations from 2 to 8 hours.[2] High clearance and redistribution after a long infusion allow a rapid return to consciousness.

The addition of an opioid to a TIVA technique decreases the propofol requirements by approximately 50%.[2] This enables even more rapid recovery after termination of the propofol and opioid infusions. The time to return of consciousness after propofol-opioid anesthesia depends predominantly on the selected opioid and only marginally on the duration of the infusion.[3] Propofol-remifentanil allows more rapid return of consciousness than propofol in combination with fentanyl, sufentanil, or alfentanil.[3,4]

Clinically, the use of TIVA has been shown to improve recovery in a number of different patient groups and settings. Propofol-based TIVA has been associated with an improved recovery profile and lower costs compared with sevoflurane for office-based anesthesia.[5] This has resulted in a shorter recovery room stay, earlier discharge, and greater patient satisfaction. However, the overall difference is small, with a total time from end of anesthesia to discharge of 51 minutes in the propofol group versus 62 minutes in the sevoflurane group.

Larsen et al compared recovery of cognitive function after propofol-remifentanil TIVA with recovery after desflurane and sevoflurane anesthesia.[6] The TIVA group exhibited significantly faster emergence than those receiving desflurane or sevoflurane, with no difference between the inhalational agents. Return of cognitive function as measured by the Trieger Dot Test and the Digit Symbol Substitution Test was significantly faster with TIVA than with desflurane and sevoflurane for up to 60 minutes after anesthesia administration. There were no significant differences between the groups at 90 minutes.

In neurosurgery, time to extubation and postoperative recovery was no different with propofol-remifentanil TIVA anesthesia than with sevoflurane-sufentanil anesthesia when both groups were guided by a bispectral-index (BIS) protocol.[7] The authors theorized that the use of BIS monitoring in both arms of the study might have blunted the pharmacodynamic advantages of TIVA. A previous study found more rapid recovery from sevoflurane than from TIVA during spinal

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surgery when anesthetic administration was guided by somatosensory-evoked potentials.[8] However, depth-of-anesthesia monitoring also has been shown to enable improved recovery and decreased propofol use during TIVA.[9,10] BIS-guided TIVA also may decrease the risk of awareness compared with routine TIVA.[11]

Recently, a large study examined the recovery characteristics of 1,158 patients undergoing mixed-day case surgery. Patients were randomized to propofol induction and maintenance (TIVA), propofol induction and isoflurane/$N_2O$ or sevoflurane/$N_2O$, or inhalational sevoflurane induction and maintenance. Depth-of-anesthesia monitoring was not used. There was less PONV with TIVA, but no difference in time to mental state on awakening, recovery time, time to discharge, or unplanned hospital admissions between the groups.[12]

TIVA had a similar recovery profile to desflurane-based inhalational anesthesia in children undergoing ear, nose, and throat procedures. However, agitation level remained high after both anesthesia methods, though there was significantly less agitation in the TIVA group (44% *v* 80%).[13] More recently, a study by Millar et al in day-case pediatric anesthesia showed similar levels of postoperative cognitive function with propofol and isoflurane.[14] Reaction time and psychomotor coordination were impaired in both groups 60 minutes postoperatively but had recovered at 24 hours. Both groups had significant impairment of visual memory both at 60 minutes and 24 hours postoperatively.

## PONV

PONV frequently complicates surgery and anesthesia, and patient surveys consistently indicate that it is one of the most unpleasant experiences in the perioperative period.[15] Despite significant advances in our knowledge of PONV, and the introduction of new antiemetic drugs, the overall incidence of PONV is estimated to be about 30%.[16] In high-risk groups, this incidence is as high as 80%.[16] Patients report avoidance of PONV to be of greater concern than avoidance of postoperative pain, and they express willingness to pay up to $100 out of pocket for an effective antiemetic.[17] PONV can cause prolonged recovery times and increased nursing care for all procedures, as well as unexpected admission after ambulatory surgery.[18] All these factors increase overall medical costs.

TIVA with propofol is associated with a lower incidence of PONV compared with inhalational agents.[19] The use of TIVA reduces the PONV risk by approximately 25%.[20] The antiemetic effect of propofol is most pronounced in the early postoperative period, with a number needed to treat = 5 to decrease PONV occurrence within the first 6 hours.[19,21] Propofol, used as part of TIVA, is effective in all patients at reducing baseline risk for PONV.[16]

A recent study found that opioid-free TIVA with a combination of propofol, ketamine, and dexmedetomidine was able to reduce the absolute risk of developing PONV by 17.3% (number needed to treat = 6) compared with inhalational anesthesia with opioids.[22] Of particular interest was the fact that both groups received triple PONV prophylaxis with a transdermal scopolamine patch, dexamethasone, and ondansetron. The effect of opioid-free TIVA was therefore in addition to best-practice antiemetic therapy.

Subhypnotic propofol also has been shown to be more efficacious than placebo for the management of PONV.[23] The median concentration of propofol associated with a 50% reduction in nausea is 343 ng/mL.[24] This can be achieved with a bolus of 10 mg propofol followed by an infusion of 10 μg/kg/min.[24] Alternatively, boluses of 20 mg of propofol administered via a patient-controlled device in the postanesthesia care unit have been shown to reduce PONV and enable earlier discharge.[23]

Although the exact mechanism of action of propofol in reducing PONV has not been elucidated, several mechanisms have been proposed, including a direct depressant effect on the chemoreceptor trigger zone, the vagal nuclei, and other centers implicated in PONV. In animal models, propofol has been shown to decrease synaptic nerve transmission in the olfactory cortex[25] and to decrease serotonin levels in the area postrema.[26]

A systematic review of 58 studies also showed that TIVA with propofol is more effective than inhalational anesthesia in reducing postdischarge nausea and vomiting (PDNV).[27] PDNV increasingly is being recognized as a significant problem, with a reported incidence of 37% in the first 48 hours after discharge following outpatient surgery.[28] PDNV can be difficult to treat, because patients can no longer receive IV antiemetic agents. The use of TIVA as part of a multimodal approach is recommended for all patients at high risk of PONV or PDNV.

## MYOCARDIAL PROTECTION

Volatile anesthetic agents have been shown to offer a cardioprotective effect due to ischemic preconditioning during coronary artery bypass surgery. A meta-analysis of 22 studies showed a significantly decreased rate of myocardial infarction and death in patients undergoing cardiac surgery with desflurane or sevoflurane when compared with TIVA.[29]

The relative cardioprotective effect of propofol is controversial. Propofol has been reported to enhance the antioxidant capacity of erythrocytes and tissues and thereby provide dose-dependent protection during ischemia and reperfusion.[30] In animal models, propofol has been shown to produce a cardioprotective effect for up to 48 hours.[31]

A retrospective study of 10,535 patients undergoing cardiac surgery concluded that sevoflurane and propofol offer some, yet different, cardioprotective properties.[32] The results of randomized controlled trials (RCTs) are contradictory. Some RCTs[33–35] have concluded that TIVA does not seem to offer any myocardial protection in patients undergoing cardiac surgery, in comparison to the volatile agents, whereas others[36–38] have found no difference when either technique was used. It is important to note that all of these studies used postoperative troponin rises as a marker of myocardial necrosis. The clinical relevance of this is uncertain. Indeed, it may be very difficult, if not virtually impossible, to extrapolate small but statistically significant decreases in biochemical markers of myocardial necrosis observed with volatile anesthetics into demonstrable improvements in outcome.

## POSTOPERATIVE PAIN

Most patients experience postoperative pain, which is associated with adverse clinical and economic outcomes. A recent study suggested about 86% of patients experienced pain after surgery; of these, 75% had moderate or extreme pain during the immediate postsurgical period, with 74% still experiencing these levels of pain after discharge.[39]

There is some emerging evidence that the type of anesthetic might affect the level of postoperative pain. Animal models have shown that volatile anesthetics cause hyperalgesia on emergence from anesthesia[40] (possibly due to inhibition of nicotinic acetylcholine receptors in the brain and spinal cord[41]) and that propofol may have a peripheral antinociceptive effect.[42]

Cheng et al compared propofol with isoflurane in 80 women undergoing uterine surgery.[43] The primary outcome variable was pain reported on a visual analog scale. They found that TIVA with propofol resulted in significantly less pain and morphine use in the first 24 hours ($p < 0.01$ for both outcomes). Conversely, in middle ear surgery, Mukherjee et al found that patients receiving TIVA experienced more postoperative pain in the recovery room and required more morphine.[44]

Most interestingly, a recent large RCT ($n = 366$) evaluating the effects of anesthesia on chronic post-thoracotomy pain syndrome (CPTS) found a significantly lower prevalence of CPTS in patients receiving TIVA with propofol-remifentanil than in those receiving inhalational anesthesia.[45] The TIVA group had less allodynia and CPTS at 3 months (38.2% *v* 56.5%, $p = 0.001$) and at 6 months (33.5% *v* 50.6%, $p = 0.002$). The authors theorized that this reduction in CPTS could be due to the following factors: the peripheral antinociceptive effect of propofol[42]; the antioxidizing effects of propofol[46]; the neuroprotective effect of propofol on injured intercostal nerves[47]; the inhibition of NMDA subtype of glutamate receptor by propofol.[48]

In addition, propofol TIVA has been shown to reduce remifentanil-induced hyperalgesia.[49] In a study by Shin et al of patients undergoing breast cancer surgery, the group receiving propofol during high-dose remifentanil-based anesthesia reported better postoperative analgesia with a significantly lower cumulative morphine consumption at 24 hours than the sevoflurane group.[49] The NMDA receptor is involved in the genesis of hyperalgesia, so this effect also may be related to NMDA receptor antagonism.[50]

## OTHER OUTCOMES

### Sinus Surgery

TIVA has been shown in some studies to affect blood loss during endoscopic sinus surgery, with consequent effects on cardiovascular stability and the visual field during surgery.[44] However, a recent meta-analysis of 42 studies found no difference in blood loss, heart rate, or blood pressure between TIVA and inhalational anesthesia.[51] Only 7 studies reported a visibility score, but they favored the TIVA group ($p < 0.001$).

### Burn Surgery

TIVA based on ketamine frequently is used for major operations requiring GA in critically ill burn patients, particularly if there is a concomitant inhalational injury. A recent study found that the use of ketamine, fentanyl, and propofol in this setting was safe and resulted in less pressor requirements (with equivalent cardiovascular stability during TIVA cases) than inhalational anesthesia.[52]

### Tracheal/Bronchial Foreign Body Removal

A recent study compared TIVA and inhalational anesthesia in children <3 years of age undergoing rigid bronchoscopy while spontaneously breathing for tracheal/bronchial foreign body removal.[53] The investigators found that inhalational anesthesia with sevoflurane provided more stable hemodynamics and respiration, as well as faster induction and recovery. In particular, the TIVA group had significantly higher rates of breath-holding (6% *v* 31%, $p < 0.05$) and desaturation (16% *v* 38%, $p < 0.05$).

### Postoperative Lung Function

Tiefenthaler et al recently performed the first study investigating the influence of anesthetic technique on postoperative lung function.[54] The study was performed in 60 patients undergoing lumbar disc surgery in the prone position. As in previous work on postoperative lung function, the investigators found that lung function parameters decreased after surgery irrespective of the type of anesthesia administered. However, the decrease in functional residual capacity was marginally greater with TIVA than with inhalational anesthesia.

## WHAT OUTCOMES ARE IMPORTANT?

With TIVA, as with any new drug, monitor, or technique, one of the major goals is to show an outcome benefit to patients. Therefore, an important first question is, what outcomes are important? Published studies to date evaluating recovery from TIVA focus on recovery times and the incidence of major and minor complications. These outcomes are important and need to be studied, but equally important and frequently ignored is the quality of recovery (QoR) from the patient's perspective.[55]

Myles et al recently developed 2 postoperative QoR scores: the comprehensive 40-item score (the QoR-40)[56] and an abbreviated version (the QoR-15).[1] The QoR-15 can be completed in less than 2 minutes and provides a valid, reliable, and easy-to-use method of measuring patient QoR. More studies in the future should include a QoR score such as the QoR-15 when assessing any new drug or technique as well as any change in health care delivery.

## FUTURE DEVELOPMENTS

There are several new sedative drugs and formulations being developed. Remimazolam is a novel, ultra-short-acting benzodiazepine derivative. In phase 1 clinical trials, median time for return to a fully alert condition was 10 minutes compared with 40 minutes for midazolam.[57]

Novel propofol and etomidate formulations are being developed in an effort to overcome drawbacks associated with current

formulations, such as pain on injection (for propofol) and adrenal suppression (for etomidate).[58] Although these agents are in early stages of development, preliminary evidence is encouraging, and they may increase the popularity of TIVA in the future.

## CONCLUSION

In summary, TIVA is superior to inhalational anesthesia for the prevention of PONV and is recommended for use as part of a multimodal regimen in all patients at high-risk of PONV. The data on recovery of anesthesia and TIVA is mixed, and the use of TIVA does not appear to produce a significantly improved wakeup. The opioid selected may be more important than the type of anesthesia, with remifentanil enabling a more rapid return of consciousness.

There is some emerging data that the use of TIVA may improve postoperative pain. In particular, the decrease in chronic pain after anesthesia with propofol is of interest; further studies are needed to investigate this association and its mechanism of action.

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