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Review Article

Influence of propofol-based total intravenous anaesthesia on peri-operative outcome measures: a narrative review

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Summary

Propofol-based total intravenous anaesthesia is well known for its smooth, clear-headed recovery and anti-emetic properties, but there are also many lesser known beneficial properties that can potentially influence surgical outcome. We will discuss the anti-oxidant, anti-inflammatory and immunomodulatory effects of propofol and their roles in pain, organ protection and immunity. We will also discuss the use of propofol in cancer surgery, neurosurgery and older patients.

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Introduction

Propofol was discovered in 1977 and introduced to clinical practice in 1986. Although initially used as an anaesthetic induction agent, it became rapidly apparent that it was suitable for infusion to produce sedation and anaesthesia (total intravenous anaesthesia (TIVA)). Manual dosing regimens were superseded by a pharmacokinetic target-controlled infusion (TCI) pump (Diprifusor™, AstraZeneca, Cambridge, UK) which made intravenous administration as simple as using a vaporiser with inhalational anaesthetic agents. Since then propofol has become generic and relatively inexpensive with newer pharmacokinetic models applicable to infants and adults pre-installed in a variety of commercial infusion pumps ('open' TCI). The development of potent, short-acting, titratable opioids, such as remifentanil, has made TIVA even easier. Despite the well-known beneficial effects on postoperative recovery, the use of TIVA/TCI remains low as evidenced in the 5th National Audit Project of the Royal College of Anaesthetists (NAP5) where TIVA accounted for only 8% of total cases in the UK and Ireland [1]. In the USA, TCI has not been approved by the US Food and Drug Administration where it is still restricted to research. It is now the only country in the world where this is the case and this has severely limited the adoption of TIVA in the USA.

In this article, we provide a comprehensive review of the anaesthetic and non-anaesthetic benefits of propofol-based anaesthesia. Propofol is a powerful hypnotic that can be used in incremental doses to produce sedation right through to general anaesthesia. Although it may be used as a sole agent for sedation, it is almost always combined with an opioid to provide the main analgesic component during general anaesthesia [2] and our discussion of TIVA throughout this review refers to propofol- and opioid-based anaesthesia. It does not include other intravenous drugs such as ketamine or dexmedetomidine, which are sometimes included in more expansive definitions of TIVA.

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of general anaesthesia with a general incidence of 30% and can rise to 80% in patients with additional risk factors [3]. Surgical patients prefer to suffer pain rather than PONV [4] and would be willing to pay considerable amounts of money for an effective anti-emetic [5]. The relative importance of PONV is generally underestimated but it can have a significant impact on postoperative care. It can delay discharge, prevent oral fluid and nutritional intake, increase treatment costs and lead to serious complications such as wound dehiscence and anastomotic leak [5]. For mechanical reasons, it can be particularly dangerous in upper gastro-intestinal and head and neck surgical procedures.

Propofol is an anti-emetic with a median plasma concentration requirement of 343 $ng.ml^{-1}$ for efficacy [6] which is much lower than the dose requirement to produce sedation or anaesthesia, which is usually > 1 $\mu g.ml^{-1}$ [7]. Based on the randomised controlled trial (RCT) conducted by Apfel et al. [8], TIVA has become a well-established component of multimodal strategies to reduce a patient's risk of PONV. A recent meta-analysis showed that TIVA reduces the relative risk of PONV by 39% (95%CI 31–47%) compared with inhalational anaesthesia [9]; this reduction is twice that reported by Apfel et al. [8], supporting consensus guidelines that recommend TIVA in order to reduce baseline PONV risk [10].

Free radical scavenging

Propofol is a phenolic derivative with the formula 2,6-di-isopropylphenol and has a structure similar to α-tocopherol (a type of vitamin E). In common with all phenol base-free radical scavengers, it acts as an anti-oxidant by reacting with free radicals to form a phenoxyl radical [11]. Tocopherols have also been suggested to reduce the risk of cancer [12]. The anti-oxidant activity is significant, fast, stable and dynamic at clinical concentrations [13, 14]. Major surgery exposes the body to immense oxidative stress caused by reactive oxygen species generated from tissue injury and ischaemia–reperfusion injuries secondary to major vascular clamping, for example, organ transplant, aortic cross clamping, flap surgical procedures and tourniquet use [15]. The sources of reactive oxygen species are multiple and include mitochondrial proteins such as cytochrome c and nitric oxide synthase released from dysregulated endothelium. This overproduction of reactive oxygen species will tip the normal redox equilibrium in the body and can result in damage to lipids, protein and DNA. The balance between the severity of oxidative stress from surgery and the anti-oxidant capacity of the body is believed to contribute to the degree of organ dysfunction and even surgical outcome in terms of complications and oncological outcomes [16], although the evidence to support a causative mechanism is still inconclusive.

Several in-vivo and in-vitro studies have proven propofol's free radical scavenging properties either by directly chelating reactive oxygen species with the formation of propofol-derived phenoxyl radicals, inhibiting lipid peroxidation or increasing the anti-oxidant defence capacity [14, 15]. In addition, several clinical studies spanning coronary artery bypass graft surgery, liver transplant and orthopaedic surgical procedures requiring tourniquet, have demonstrated that the use of propofol as the anaesthetic agent reduced the serum levels of malondialdehyde, which is a metabolite of lipid peroxidation [17–19]. Other mechanisms that have been linked to propofol's potential organ protective effect include anti-apoptosis via the suppression of pro-apoptotic protein Bax and an anti-inflammatory effect via inhibition of macrophage production of tumour necrosis factor (TNF) α and interleukins [20, 21].

Organ protection

Cardiac

Inhalational anaesthetic agents are thought to convey protection against myocardial ischaemia–reperfusion injury via the reperfusion injury salvage kinase and the survivor-activating factor enhancement pathways [22]. This was supported in a clinical study showing that a sevoflurane-based anaesthetic technique in coronary artery surgery resulted in lower troponin levels, shorter hospital stays and, possibly, 1-year mortality, when compared with TIVA [23]. This benefit was extrapolated to patients with cardiac disease undergoing non-cardiac surgery leading the American Heart Association (AHA) to recommend inhalational-based anaesthesia for these patients in 2007 [24]. However, there have been a similar number of trials since 2007 showing no difference in postoperative troponin levels. A Scandinavian registry of 10,535 patients undergoing a variety of cardiac surgical procedures showed that patients with pre-operative unstable angina and/or recent myocardial infarction, and thus already 'preconditioned,' did not show any difference in mortality between anaesthetic groups, and lower postoperative mortality was only seen after sevoflurane in those without these predictors (2.28% vs. 3.14%; $p = 0.015$) [25]. Patients suffering pre-operative myocardial ischaemia actually benefited from propofol anaesthesia, perhaps related to its anti-oxidant effects. Cardiopulmonary bypass itself causes

reperfusion injury that, when most severe, is clinically manifested as a systemic inflammatory response syndrome. The use of propofol during bypass is associated with a less adverse inflammatory profile than isoflurane, as shown by lower levels of cytokines and inflammatory biomarkers up to 24 h post-surgery [26]. These more recent data led to a change in recommendation by the AHA in 2014 and they are now equivocal about the anaesthetic technique for patients with cardiac disease [27]. The heterogeneity in study results has been attributed to differences in surgical technique and administration pattern of the anaesthetic. In addition, the study cohorts have generally been inadequately powered to look at clinical outcomes such as myocardial infarction and mortality, hence using surrogate measures of myocardial injury. A recent trial published in 2019 is the largest and most recent trial looking at inhalational vs. intravenous anaesthesia for patients undergoing a single-vessel coronary artery bypass graft and it showed no difference in 1-year mortality [28]. A recent meta-analysis focusing on valve surgery showed similar results [29]. Thus, although there are plausible mechanistic reasons that various anaesthetics may protect against myocardial injury and clinical evidence from surrogate markers of such damage, no specific anaesthetic technique has been shown to reduce mortality, morbidity or affect long-term outcome in patients at risk of myocardial ischaemia undergoing cardiac surgery [30, 31].

Kidney

Several animal studies creating models of renal ischaemia–reperfusion injury have shown that propofol reduces biomarkers of injury via adenosine triphosphate-sensitive potassium (KATP) channels, activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signal pathway and transforming growth factor beta-activated kinase 1 (TAK1) [32–34]. This biological plausibility has not been extensively studied and clinical studies are still limited [35]. A study of 112 patients undergoing cardiac valve surgery showed that propofol-based anaesthesia reduced the incidence of acute kidney injury (AKI) by more than a third when compared with sevoflurane [36]. The severity of AKI in the propofol group, when it did occur, was also reduced. However, other studies have shown no difference in renal outcomes [37] and it has been suggested that propofol dose, baseline renal function and definition of AKI are potential contributing factors. A retrospective study in critically ill patients showed a reduction in the need for renal replacement therapy when propofol was used as sedation when compared with midazolam, suggesting possible renal protection [38]. Nieuwenhuijs-Moeke et al. showed higher urinary biomarkers of renal injury in living donor kidney transplantation on the second day after transplantation in patients receiving sevoflurane compared with propofol anaesthesia, but this damage was not reflected in inferior graft outcome [39].

Brain

Propofol reduces cerebral metabolic rate and preserves flow metabolism coupling in the brain, with cerebral autoregulation preserved at doses up to 300 $\mu g.kg^{-1}.min^{-1}$ [40, 41]. Inhalational anaesthetics not only reduce cerebral metabolic rate but they also cause dose-dependent cerebral blood vessel vasodilation and impairment of cerebral autoregulation. However, with modern inhalational agents this effect is minimal at standard clinical concentrations and in the presence of normocapnia, with cerebral autoregulation preserved at concentrations of up to 1.5 minimum alveolar concentration (MAC) sevoflurane [42] and 1.0 MAC desflurane [43].

A meta-analysis in patients undergoing craniotomy showed that propofol maintained anaesthesia results in lower intracranial pressure and higher cerebral perfusion pressure [44]. However, there were insufficient data to allow analysis of clinical outcomes, such as neurological recovery or mortality. A systematic review by the Cochrane group showed that emergence time in patients undergoing surgery from brain tumours was similar for sevoflurane and propofol anaesthesia, although none of the identified studies were of high methodological quality [45].

Several preclinical studies have suggested theoretical neurophysiological benefits of propofol; clinical doses of inhalational anaesthetics may induce caspase activation, apoptosis, Aβ oligomerisation and accumulation, neuroinflammation, tau protein hyperphosphorylation, mitochondrial dysfunction and impairment of learning and memory [46–48]. This has been reviewed in detail elsewhere [49, 50]. These changes are a pathological feature of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, and in-vitro studies, using nuclear magnetic resonance imaging, have indicated that halothane interacts specifically with Aβ peptide to induce oligomerisation and that Aβ 42 oligomerises faster than Aβ 40 [51]. Propofol only increases oligomerisation at supra-clinical doses [46] and may even attenuate isoflurane-induced caspase-3 activation and Aβ oligomerisation [52]. Despite the apparent physiological and cellular advantages, clinical research has not conclusively demonstrated a benefit in terms of postoperative cognitive function [53]. This may reflect physiological resilience as studies have also

suggested that patients with pre-existing mild amnestic cognitive impairment may be particularly vulnerable to progression after sevoflurane compared with either propofol or regional anaesthesia [54]. Emergence delirium, however, appears to be less common after propofol anaesthesia particularly in children and compared with sevoflurane [55, 56]. Metabolomic profiling can elucidate cellular events by measuring products of metabolism from the brain in real time with proton magnetic resonance spectroscopy. Cerebral metabolomic signatures are different in children anaesthetised with sevoflurane vs. propofol (sevoflurane produces higher lactate and glucose) and brain glucose and lactate concentrations are correlated with the propensity to exhibit emergence delirium. Sevoflurane-induced enhanced cortical activity in the unconscious state may interfere with rapid return to 'coherent' brain connectivity patterns required for normal cognition upon emergence of anaesthesia [57].

Pain

Although the observation that propofol reduces pain after surgery was serendipitous [58], there are clear mechanistic reasons to explain this phenomenon. Propofol exerts a positive modulation of the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) through $GABA_A$ receptors and this is believed to mediate most of its anaesthetic effect [59]. Propofol also has actions on other receptors that play a role in pain signalling; in-vitro studies have found that propofol inhibits the phosphorylation of a subunit of the *N*-methyl-D-aspartate (NMDA) receptor leading to reduced glutamatergic transmission [60] which may play an important role in the central sensitisation of pain [61]. The anti-oxidant and anti-inflammatory effects of propofol [62] are also believed to mediate part of its analgesic effect. A meta-analysis of randomised, controlled trials has shown that propofol was associated with reduced pain scores 24 h after surgery when compared with inhalational anaesthesia [63]. Other studies have also reported a reduction in pain scores and morphine consumption after surgery [64, 65]. However, although the differences in pain in these studies (measured using numeric rating scales (NRS)) reached statistical significance, the absolute differences were small (< 1 on NRS) suggesting that the benefits may not be clinically-relevant.

Propofol-based anaesthesia may also affect the incidence of chronic postsurgical pain. Chronic pain after peripheral nerve injury is associated with afferent hyperexcitability and upregulation of hyperpolarisation-activated, cyclic nucleotide-regulated (HCN) pacemaker currents in sensory neurons. There are four types of HCN channels which are ubiquitously expressed and propofol selectively inhibits HCN1-rich cells in the peripheral nervous system, sparing the cardiac pacemaker current (carried mostly by HCN2 and HCN4) and the central nervous system (where all four isoforms are expressed). In a peripheral nerve ligation model of neuropathic pain, sub-hypnotic propofol was antihyperalgesic [66]. In a study of chronic postsurgical pain, TIVA with propofol and remifentanil reduced the incidence of chronic post-thoracotomy pain syndrome at 3 and 6 months when compared with sevoflurane [67]. Similar results have also been seen after hysterectomy [68]. It is likely, therefore, that propofol-based anaesthesia plays a role in reducing both acute and chronic postoperative pain, although the latter may be of greater clinical importance.

Propofol and the immune system

Surgery and its associated stress response causes multisystem injury resulting in a wide range of endocrine, immune and haematological effects. After major surgery, there will be an increased release of cytokines such as interleukin-1(IL-1) and TNF-α. This, in turn, will induce more cytokine release, in particular IL-6, the principal mediator of the subsequent acute phase response [69]. Surgery and the stress response have been proven to suppress the activity of the cell-mediated immune system, particularly natural killer cell activity, and this immunosuppression is directly proportional to the magnitude of surgery and trauma produced. In addition, there are various other causes of peri-operative immunosuppression such as hypothermia, blood transfusion and pain-induced activation of the hypothalamic–pituitary–adrenal axis [70].

Propofol has immunoprotective effects that are mediated through a variety of pathways: it is anti-inflammatory and able to inhibit cyclooxygenase (COX)-2, reducing the production of prostaglandin E2 (PGE-2); it preserves the function of natural killer cells which are substantially downregulated by the surgical stress response [71]; it diminishes the production of cytokines (IL-1, TNF-α and IL-6) [72, 73]; and it enhances activation and differentiation of peripheral T-helper cells which augment cellular immunity [74]. Overall, propofol has been shown to produce a protective effect on the immune system which may have a positive role in improving patient outcomes, especially after major surgery.

TIVA in special patient populations

Oncology surgery

According to the World Cancer Report, global cancer cases are projected to increase by 50% from 2012 to 2030.

Similarly, a rise in cancer deaths by 60% is anticipated during the same period [75]. Around 80% of patients will require some sort of surgical intervention during their treatment and cancer surgery is associated with significant morbidity and mortality, especially for patients who present with advanced malignancy or who have pre-existing comorbidities. There are many factors that can influence the outcomes of cancer surgery, such as pre-operative chemoradiotherapy, timing of surgery and the surgical approach. The aforementioned are not under the direct control of the anaesthetist but others are, such as anaesthetic choice and the patients' ability to return rapidly to intended oncological therapy. The stress response from surgery will result in immunosuppression but a competent immune system, particularly natural killer cells, is required to recognise tumour cells as 'non-self' and destroy them, sometimes even before they become clinically detectable. Another critical factor for tumour growth and spread is neovascularisation which is mediated by vascular epidermal growth factor and transforming growth factor (TGF)-β. Vascular epidermal growth factor levels increase after surgery, with a greater concentration seen in the surgical site and this is proportional to the tissue damage induced by the operation [76, 77]. Surgery will also promote the release of matrix metalloproteinase (MMP) which will increase the motility and invasive capacity of free tumour cells [78]. Inhalational anaesthetics will upregulate hypoxia-inducible factor (HIF-1α) in tumour cells and promote new vessel formation which is linked with adverse patient prognosis [79]. In addition, sevoflurane is shown to alter the secretion of cytokines (IL-1β and TNF-α) by natural killer and natural killer-like cells in-vitro [80]. Nitrous oxide inhibits haematopoietic cell formation which depresses neutrophil function and reduces mononuclear cell function [81]. In animal models, nitrous oxide exposure is linked with escalation of the development of lung and liver tumour secondaries and, in fact, was the most potent stimulator of liver metastasis of all anaesthetic drugs evaluated in that study [82]. However, extrapolation of the above to human clinical data is more difficult to interpret because there are many confounding factors peri-operatively.

As stated earlier, propofol tends to relatively preserve immune function and does not suppress cytotoxic activity of natural killer cells. Furthermore, it is directly involved in the regulation of both microRNAs, long non-coding RNAs and various signalling pathways that serve to decrease cancer development [83]. Multiple studies have attempted to compare the outcomes of tumour surgery with the use of propofol-based TIVA or inhalational anaesthetic agents. The largest propensity-adjusted, retrospective analysis showed that mortality was nearly 50% greater with inhalational than with propofol anaesthesia [84]. In another systematic review, statistical analysis of three retrospective studies, including a total of 10,193 patients, supported the hypothesis that TIVA is more favourable for cancer survival [85]. A recent meta-analysis also suggested that TIVA is linked with enhanced recurrence-free survival and overall survival in patients undergoing cancer surgery [86]. Another recent study found less unplanned intensive care unit admission after thoracic lung resection surgery in patients receiving TIVA [87]. Based on this evidence, TIVA does appear to be the preferred anaesthetic especially in patients undergoing cancer surgery and, consequently, there are a number of large prospective multicentre studies currently ongoing which should provide a definitive answer. It should also be remembered that the ability to return to intended oncological therapy plays an important role in cancer treatment after surgery and, as discussed elsewhere in this review, propofol anaesthesia may be advantageous in this regard [88].

Neurosurgery

As discussed earlier, TIVA with propofol and remifentanil offers theoretical advantages for neurosurgical procedures, most notably rapid, smooth emergence with early recovery of cognitive function [89]. Higher activity in the cortex during sevoflurane anaesthesia, when compared with propofol, may also account for the delay in return to coherent brain connectivity presenting as delirium when emerging from inhalational anaesthesia [57], although results from clinical studies have shown conflicting results [89, 90]. Rapid, coherent, smooth emergence without vomiting is important for neurosurgical patients so that any change in neurological status caused by surgery or progression of underlying pathology can be assessed rapidly. This is particularly important during the awake phase of awake craniotomy, as the patient has to undergo a battery of tests to map out pathological and eloquent areas. Most of the studies in a systematic review on anaesthesia management for awake craniotomy utilised propofol as part of the anaesthetic regime, showing TIVA as the de facto technique for awake surgery [91].

Another major indication for TIVA in neurosurgery is when intra-operative neurophysiological monitoring is considered, with somatosensory-evoked potential and motor-evoked potential being the most common modalities. Inhalational anaesthesia causes a much greater dose-dependent depression of the evoked responses than propofol [92] making TIVA the recommended anaesthetic technique in various position statements [93, 94]. Total

intravenous anaesthesia with remifentanil is able to provide immobility during surgery without affecting neuromuscular junction transmission, thus allowing compound muscle action potentials such as in electromyography and motor-evoked potential to be properly monitored. Motor-evoked potentials are particularly sensitive to inhalational agents and studies have shown that the presence of inhalational agents increased the stimulation threshold required and failure rate [95, 96]. The cortical response during somatosensory-evoked potential monitoring is particularly depressed by inhalational agents making them even more undesirable for intracranial neurosurgery because this may be the only monitoring site available distal to a subcortical surgical site [97]. This is different in spinal surgery, as preservation of either the cortical or subcortical response will mean that the sensory-evoked potentials have passed through the spinal cord, thus confirming its integrity.

Older patients

Older patients are more susceptible to the adverse effects of both surgery and anaesthesia as they have less physiological resilience and greater incidence of comorbid medical conditions [98]. This will complicate the peri-operative journey as the complexity of cases increases and will, invariably, result in a higher incidence of unfavourable postoperative outcomes. Furthermore, pharmacodynamic sensitivity to anaesthetic agents also increases with age [99]. For inhalational agents, there is a decline in MAC by 0.6% each year after the age of 40 [100]. A similar phenomenon is observed with intravenous anaesthetic agents as pharmacokinetics is altered such that the clearance of many drugs is reduced while pharmacodynamic sensitivity increases. Consequently, some clinicians may have reservations in administering TIVA to older patients for fear of overdose or hypotension [101], or because most pharmacokinetic models used for TCI were developed in young, healthy individuals [102]. However, there is no evidence to indicate that propofol-based TIVA is unsafe or harmful in older patients. As per recommendations, titration to clinical effect is very important [103] and is, in fact, a clear advantage of TIVA. Lack of familiarity with this technique was suggested by a retrospective study showing that clinicians often administer larger than recommended doses of propofol to older patients resulting in more pronounced dose-dependent effects [104]. A Cochrane review stated that neither inhalational agents nor propofol-based TIVA affects 30-day mortality or duration of hospital stay in patients aged > 60 years undergoing non-cardiac surgery [53]. There was, however, low-certainty evidence that maintenance with propofol-based TIVA reduces peri-operative neurocognitive disorder. As mentioned earlier, propofol exhibits anti-inflammatory effects, free radical scavenging and preserves cerebral autoregulation [105]. The neuroprotective effects have also been demonstrated in diverse models of neuronal injury and it is also less likely to exert neurotoxic effects than conventional inhalational agents [106]. Total intravenous anaesthesia can be safely administered to older patients by choosing a lower effect-site concentration (C_e) to start with and then titrating slowly to the desired anaesthetic depth with small increments in C_e. Titration and intra-operative monitoring can be assisted with processed electroencephalography (EEG) which can both help avoid accidental overdosing and reduce the risk of postoperative delirium and POCD [107]. As such, compared with inhalational anaesthesia, TIVA has several theoretical benefits in older patients, especially for those who are at risk of developing postoperative neurocognitive dysfunction, such as those with dementia [108].

Why has inhalational anaesthesia persisted for so long?

The development of inhalational anaesthesia was a huge medical advance at the time. Anaesthetic drugs are exceptionally dangerous by virtue of their intended use and have a very low therapeutic index. Being able to administer these drugs by inhalational titration, relatively safely, was a healthcare revolution that paved the way for surgery as we now know it. Despite the advent of infusion pumps, computers and sterile intravenous drugs, the inhalational route of anaesthesia has become ingrained and pharmaceutical companies continue to produce new drugs based on this legacy. Inhalational anaesthesia is one of the fundamental skills that every new anaesthetic trainee will first master and TIVA seems to be considered as an 'advanced' competency, even though all anaesthetists should be capable of using it [103]. Inhalational agents do have certain advantages in that administration is relatively simple, potency in terms of MAC is familiar and end-tidal concentrations can be measured in real time. New agents such as sevoflurane and desflurane have a fairly quick onset and offset of action. In the UK and Ireland, only 8% of anaesthetics are performed using TIVA [1] and two recent surveys have helped to elucidate some of the reasons for this, many of which are related to training and education [109, 110]. For example, cost is often stated as an issue against TIVA but, with the availability of generic propofol and open TCI systems, TIVA can actually be markedly cheaper than using sevoflurane and desflurane [111], without factoring in the extra costs that may arise from poor recovery.

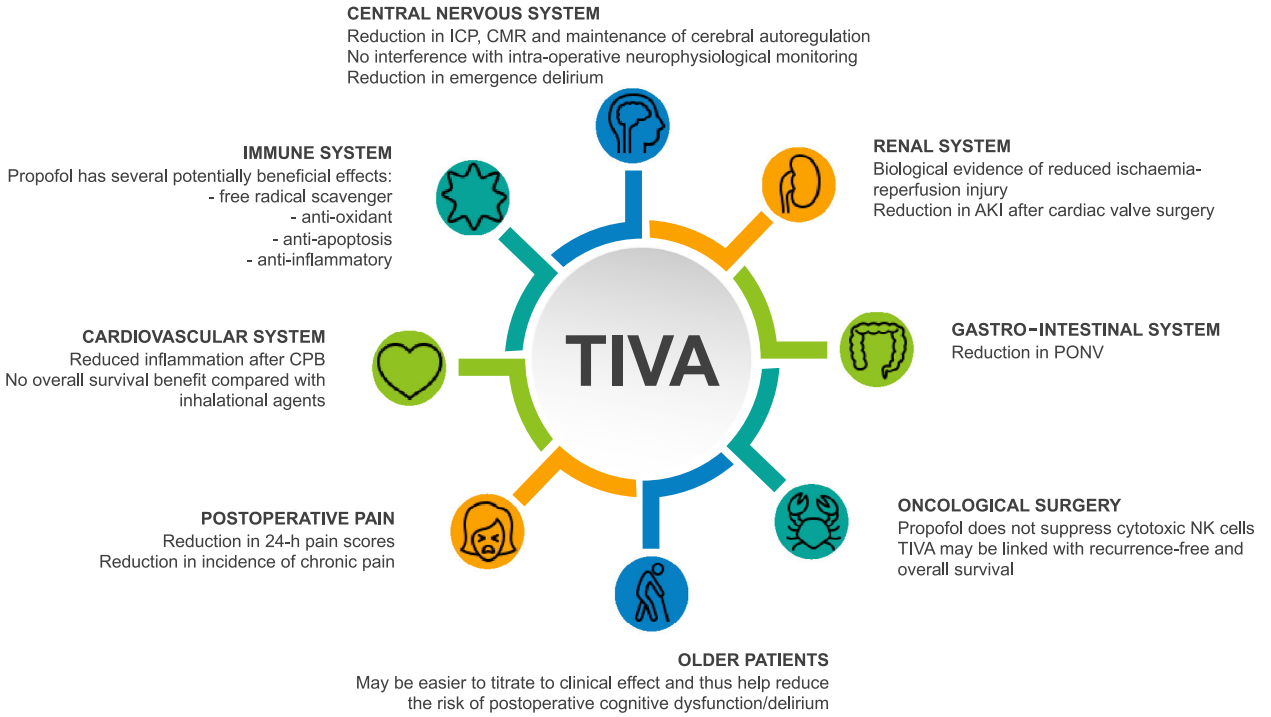

Figure 1 A summary of the potential benefits of propofol-based TIVA. TIVA, total intravenous anaesthesia; ICP, intracranial pressure; CMR, cerebral metabolic rate; AKI, acute kidney injury; CPB, cardiopulmonary bypass; PONV, postoperative nausea and vomiting; NK, natural killer.

It is important to mention that the incidence of awareness during general anaesthesia is nearly twice as high during TIVA compared with inhalational anaesthesia particularly when neuromuscular blocking agents are used, although the overall incidence is still very low [1]. Accidental awareness under general anaesthesia is commonly related to errors in administration and it is apparent that better education is required. Recently published guidelines [103, 112] go some way to helping with this but we believe workshops and more practical training are necessary [113]. Most of the recommendations outlined in the Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia [103] are related to enhancing the safety of intravenous drug delivery such as the design of infusion sets, standardisation of drug regimen and the use of a processed EEG as a further guide of monitoring, especially in situations where neuromuscular blocking drugs are used. When propofol-based TIVA is used to maintain general anaesthesia, it is strongly recommended to deliver the drug via a TCI pump as these are able to obtain and maintain accurate steady-state plasma concentrations in both clinical and validation studies [114–117]. Commonly used pharmacokinetic models are Schnider and Marsh [118, 119] for propofol and Minto [120] for remifentanil infusion. Discussion of the relative merits of these models is beyond the scope of this review but clinicians should become familiar with one model and learn how to titrate it. There are also models commercially available for children [121, 122] and various methods for administering TIVA in obese patients [123]. The recent publication of the Eleveld model is a promising development for more accurate TCI [124]. Processed EEG, despite its own limitations, may be helpful in titrating anaesthetic depth [125] and now there are even closed-loop anaesthesia delivery systems that can titrate TCI according to EEG parameters [126].

Conclusion

Modern anaesthesia is still mostly administered by the inhalational route but there is increasing concern over their potential for pollution and other adverse effects. Exposure to halogenated hydrocarbons may cause reduction in anti-oxidant activity in plasma and erythrocytes, inhibition of neutrophil apoptosis, depression of central neurorespiratory activity, increased DNA breaks, effects on cerebral blood circulation and altered renal function. There are other disadvantages of inhalation drugs that can be avoided or reduced with propofol such as inhibition of hypoxic vasoconstriction, increased intracranial pressure, administration practicalities (laryngoscopy, bronchoscopy, jet

ventilation), malignant hyperthermia and PONV. Propofol has anti-inflammation and powerful anti-oxidant properties which are organ protective and may contribute to the better analgesia seen after surgery compared with inhalation anaesthesia. The peri-operative period creates a perfect storm of inflammation, immunosuppression and tumour cell liberation to drive cancer recurrence and metastasis. Propofol has been shown to inhibit HIF-1α activity. This and the anti-oxidant effects could explain the dramatic difference in postoperative survival seen in retrospective studies of cancer surgery that are currently being studied in a number of randomised, controlled trials. The advent of remifentanil, generic preparations of propofol and refinements to its lipid vehicle make TIVA economically attractive. The potential advantages of propofol are illustrated in Fig. 1. Easy to use commercially available target-controlled drug delivery systems have simplified TIVA making it as simple as using a vaporiser. Total intravenous anaesthesia is, therefore, a mainstream anaesthetic technique that all anaesthetists should be familiar with and more practical teaching should be prioritised in training programmes.

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