



Are there beneficial effects to hybrid anesthesia*?

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Abstract

As the COVID-19 pandemic increased the use of propofol in the intensive care unit for the management of respiratory sequelae and supply had become a major issue. Indeed, most hospitals in Japan were forced to use propofol only for induction of anesthesia with inhalational maintenance. Large amounts of propofol remain in the syringe which exacerbates the problems by increased waste. I propose that use of low dose propofol in combination with a low concentration inhaled anesthetic as an alternative and call this hybrid anesthesia. Several advantages of hybrid anesthesia are evident in the literature. Volatile anesthesia has several disadvantages such as cancer progression, emergence agitation, marked reduction in motor evoked potentials (MEP), laryngospasm with desflurane and postoperative nausea and vomiting (PONV). Volatile anesthesia exerts some beneficial actions such as myocardial protection and fast emergence with desflurane. In contrast, total intravenous anesthesia (TIVA) provides better survival in patients undergoing radical cancer surgery, reduction in emergence agitation, laryngospasm, PONV and better MEP trace. Intraoperative awareness occurs more often during TIVA. When intravenous and volatile anesthesia are combined (hybrid anesthesia), the disadvantages of both methods may be offset by clear advantages. Thus, hybrid anesthesia may, therefore, be a viable anesthetic choice.

Keywords Total intravenous anesthesia · Volatile anesthesia · Hybrid anesthesia

Background

The COVID-19 pandemic increased the use of propofol in the intensive care unit (ICU) for management of respiratory sequelae and consequently strained supply in many countries [1, 2]. To manage this situation and preserve supply for ICU, most hospitals in Japan were forced to use propofol only for induction of anesthesia with inhalational maintenance. Large amounts of propofol remain in the syringe which exacerbates the problem by increased waste. I propose the use of low dose propofol in combination with a low concentration inhaled anesthetic as an alternative and call as hybrid anesthesia. Several advantages of hybrid anesthesia are already evident in the literature and this review evaluates these (Fig. 1).

Disadvantage of volatile anesthesia

Cancer progression

Clinical study Many retrospective clinical studies strongly indicate that total intravenous anesthesia (TIVA) may provide better postoperative outcome such as long-term survival after cancer surgery compared to inhalational anesthesia [3–6] while prospective studies failed to confirm this [7, 8]. Although it is not clear from clinical studies whether inhalation anesthesia has a cancer-promoting effect, clinical studies using patient's samples showed that TIVA may be preferable for cancer patients compared to inhalational anesthesia [9–11]. Looney and colleagues [9] studied effects of anesthetic methods (volatile anesthesia vs propofol TIVA with paravertebral block) on serum cancer-related factors such as VEGF-C and TGF- β 1 in patients undergoing radical breast cancer surgery. It is known that VEGF-C is involved in breast cancer growth and TGF- β 1 inhibits breast cancer growth in the early stage. They found that VEGF-C was significantly increased and TGF- β 1 was significantly decreased in the sevoflurane anesthesia group, while TGF- β 1 was significantly increased in propofol TIVA with paraverte-

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bral block group. Using patient blood samples, the same research group treated MDA-MB-231, an estrogen receptor (-) breast cancer cell [10] with serum obtained after surgery. They found that apoptosis of the cancer cells progressed in the propofol TIVA with paravertebral block group, whereas apoptosis was suppressed in the sevoflurane group. Ferrell and colleagues [11] used human tissue samples to determine effects of anesthetic agents on oncogene expression. Pre-anesthetic samples were obtained from a preoperative tumor biopsy and postanesthetic samples were from extirpated tumors. They found a significant increase in the expression of cytoplasmic HIF-2 α and nuclear p-p38 MAP kinase by sevoflurane anesthesia but not by TIVA. These data indicate that inhalational anesthetics do not have any beneficial effects on cancer patients.

Basic research Volatile anesthetic agents: Basic studies clearly show pro-cancer effects of volatile anesthetics [12]. Why does volatile anesthesia cause pro-cancer actions? It is known that volatile anesthetics induce significant upregulation of hypoxia-inducible factor 1 α (HIF-1 α), which plays major roles in tumor angiogenesis, metastasis, and proliferation [12].

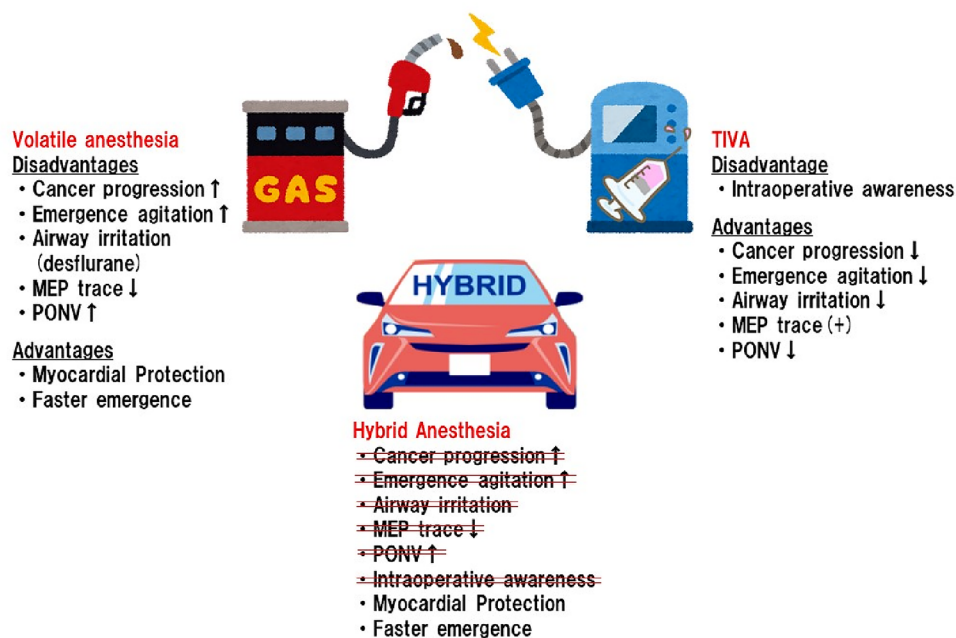
Intravenous anesthetic agents: We previously reported that ketamine concentration-dependently reduced proliferation of C6 glioma cells but did not change that of rat neonatal astrocytes (normal cells) [13]. Similarly, the NMDA antagonist MK801 could exert a concentration-dependent antiproliferative effect in human tumor cell lines but not in human bone marrow stromal cells [14]. In addition, MK801 significantly

inhibited tumor proliferation of both neuroblastoma and rhabdomyosarcoma in nude mice when these tumor cells were inoculated into the right flank [15], Propofol may also exert anti-cancer actions. Matsumoto and colleagues [16] found that propofol concentration dependently inhibits the migration of several cancer cells in vitro and 40 mg/kg/day of propofol significantly reduced pulmonary metastasis whilst primary tumor size did not change compared to that with vehicle. Several mechanisms have been proposed for the anticancer effects of propofol. Miao and colleagues [17] reported that GABA_A receptors may be involved as bicuculline completely inhibited propofol anti-cancer effects. Inada and colleagues [18] suggested that inhibition of COX₂ by propofol may also be involved in the mechanism as inhibition of COX₂ reduces PGE₂ release from macrophage, and the reduction subsequently increases INF γ production from NK cells. In addition, increases in caspase activity by propofol may also be involved as an increase in caspase activity cause cancer cell apoptosis [19].

Emergence agitation

It is known that children are more likely to experience emergence agitation after volatile anesthesia than following propofol-TIVA [20]. Similar to that seen in children volatile anesthesia significantly caused emergence agitation compared to TIVA in adults [21]. Even when volatile anesthesia is used, emergence agitation may be reduced by a regional anesthesia technique. Wang and

Fig. 1 Advantages of hybrid anesthesia. Hybrid anesthesia can eliminate the disadvantages of volatile anesthesia and TIVA, while retaining the advantages of both anesthetic methods



colleagues [22] found that infraorbital nerve blocks significantly reduced emergence agitation after sevoflurane anesthesia in children undergoing cleft lip surgery. The nerve block also reduced sevoflurane concentration required for surgery.

Desflurane and airway problems

Zwass and colleagues [23] compared airway effects of desflurane and halothane anesthesia induction in children. They found that most patients had no or only mild airway complications during induction in the halothane group while more than half of the patients experienced coughing, laryngospasm, and breathlessness in the desflurane group. Animal studies also showed that desflurane above 1 minimum alveolar concentration (MAC) could induce airway contraction in a biphasic manner.

Motor-evoked potentials (MEP)

A practical guide provided by Japanese Society of Anesthesiologists [24] describe that at a sedation level of bispectral index (BIS); a value of 50, the amplitude of motor evoked potentials (MEP) under propofol anesthesia were twice that under sevoflurane or desflurane anesthesia. If sufficient MEP amplitude cannot be recorded with inhalational anesthesia, switching to propofol TIVA should be considered.

Postoperative nausea and vomiting (PONV)

Wu and colleagues [25] retrospectively compared PONV between desflurane anesthesia and propofol TIVA in ophthalmic surgery patients, and found that the incidence of PONV in the propofol TIVA group was one-third of the desflurane anesthesia group. A meta-analysis of the incidence of PONV for propofol and inhalation anesthesia shows that propofol anesthesia has less PONV than inhalation anesthesia [26].

Advantages of volatile anesthesia

Myocardial protection

A meta-analysis has shown that postoperative cardiac output is significantly higher in coronary artery bypass grafting (CABG) or off-pump coronary artery bypass grafting (OPCAB) patients with sevoflurane anesthesia than with propofol TIVA, even at 12 h postoperatively [27]. In addition, postoperative myocardial troponin I levels, indicative of myocardial damage, were significantly lower in the sevoflurane anesthesia group in CABG patients. On the other hand, there was no difference between

sevoflurane anesthesia and propofol TIVA in patients undergoing OPCAB and aortic valve replacement. De Hert and colleagues [28] reported that the effect of inhalational anesthesia on postoperative cardiac function in CABG patients compared to that of propofol TIVA, desflurane and sevoflurane anesthesia provided significantly higher cardiac index than propofol TIVA. The results were similar to those with sevoflurane anesthesia. The number of patients who required catecholamine support after cardiopulmonary bypass and in the intensive care unit (ICU) was significantly lower with desflurane ($n=4$ and 5) and sevoflurane anesthesia ($n=3$ and 4) than propofol TIVA ($n=10$ and 12), respectively. Thus, desflurane and sevoflurane anesthesia caused less postoperative cardiac depression. They also found that blood troponin I was significantly lower in desflurane and sevoflurane anesthesia than that in propofol TIVA. Guarracino and colleagues [29] found similar results in OPCAB patients where postoperative myocardial troponin I levels remained significantly lower in the desflurane anesthesia group compared to the propofol TIVA group. Thus, desflurane appears superior to propofol TIVA for myocardial protection.

Faster emergence

Wachtel and colleagues [30] performed a meta-analysis of average times and variability in times to extubation and to respond to commands after desflurane anesthesia and propofol TIVA. They found that desflurane can provide earlier time to both extubation and response to commands with a reduction in the variability in the times. Thus, the time of emergence from general anesthesia can be easily predicted.

Can the disadvantages of volatile anesthesia be overcome?

The problems of volatile anesthesia including with desflurane can be mitigated if the concentration can be reduced. Indeed, expression of cancer-related genes such as hypoxia inducible factor-1 α and 1 β , vascular endothelial growth factor, heme oxygenase 1 and inducible nitric oxide synthase, desflurane-induced airway constriction, emergence agitation may not occur with concentrations less than 1 MAC [22, 31, 32]. The combination of volatile anesthesia with regional anesthesia [33], remifentanyl infusion [34] and/or intravenous anesthesia (= hybrid anesthesia) [35] can reduce the volatile anesthetic concentration to less than 1 MAC. Lu and colleagues [33] reported that the desflurane concentration required was reduced by about 40% with epidural block compared to that without when the A-line™ ARX index was used to adjust the depth of anesthesia in patients undergoing colorectal surgery under

desflurane anesthesia with or without epidural block. Shin and colleagues [34] found that remifentanyl target-controlled infusion (TCI) at 1 and 2 ng/ml reduced desflurane concentration from 7.9 ± 0.5 to 5.2 ± 0.5 and $4.4 \pm 0.5\%$, respectively. Harris et al. [35] examined whether the interaction between sevoflurane and propofol was synergistic or additive using the Dixon up-down method for loss of consciousness and noxious stimuli in 36 patients undergoing elective surgery. They found that the interaction between sevoflurane and propofol was additive and propofol-TCI at 1.2 $\mu\text{g/ml}$ is equivalent to 0.3 MAC of sevoflurane.

Advantages of hybrid anesthesia

Emergence agitation

Liang and colleagues [36] studied the efficacy of hybrid anesthesia (sevoflurane-propofol). In this study, 160 patients undergoing elective gastrointestinal surgery were equally assigned to sevoflurane-epidural anesthesia and hybrid-epidural anesthesia groups ($n=80$ each). The results showed that emergence time including time to verbal response and time to extubation was significantly faster in the hybrid-epidural anesthesia group than that in sevoflurane-epidural anesthesia group. In addition, emergence agitation was significantly less in the hybrid anesthesia-epidural group.

MEP

Yang et al. [37] studied the efficacy of additional remifentanyl, fentanyl, or propofol-remifentanyl on MEP during sevoflurane anesthesia. They found that sevoflurane concentration was reduced to less than 1% by the addition of opioids or propofol, resulting in MEPs that were comparable to those recorded with propofol TIVA in pediatric spine surgery.

PONV

Kawano and colleagues [38] determined which anesthetic method was superior with respect to PONV. The enrolled 126 laparoscopic gynecologic surgery patients who were divided into 3 groups of 42 each: sevoflurane, propofol-TIVA, and propofol/sevoflurane hybrid anesthesia groups. Depth of anesthesia was adjusted to achieve a BIS value of 40–60 in each group. The results showed that PONV in the hybrid anesthesia group was significantly lower than that in the sevoflurane group and comparable to that of the propofol TIVA group.

Prevention of intraoperative awareness

Yu and colleagues [39] examined intraoperative awareness in 1244 surgical patients assigned to propofol TIVA ($n=566$) or hybrid anesthesia with propofol/sevoflurane ($n=678$). They found that intraoperative awareness was significantly less in the hybrid anesthesia group [0.44% ($n=3$)] compared to propofol TIVA [1.94% ($n=11$)]. These data suggest that the addition of volatile anesthesia to propofol can significantly prevent intraoperative awareness.

Prevention of cough reflex

Lai and colleagues [40] reported on 90 video-assisted thoracoscopic surgery (VATS) patients divided into two groups: propofol TIVA and hybrid anesthesia (propofol-sevoflurane) groups ($n=45$, each). VATS surgery was performed under spontaneous respiration with a laryngeal mask insertion. The results showed that the hybrid anesthesia was more effective than propofol TIVA to suppress the cough reflex during VATS surgery.

Conclusion

In general, a simple anesthesia technique is considered better. However, when intravenous and volatile anesthesia are combined, the disadvantages of both methods may be offset with clear advantages. This review clearly demonstrates “beneficial effects to hybrid anesthesia”. Hybrid anesthesia may, therefore, be a viable anesthetic choice.

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Declarations

Conflict of interest Main content of this article was presented at Baxter Ltd (desflurane distributor in Japan) sponsored lecture in the 28th annual meeting of Japanese Society for Intravenous Anesthesia held in Fukui, November 27, 2021.

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