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MINI-REVIEW

Inhalational *vs*. Intravenous anesthesia: is opposition helpful for clinicians?

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Abstract

An intense debate focusing on the polluting effect of volatile anesthetics has recently called into question their role and importance, even though they have been fundamental to general anesthesia until now. In this brief narrative review, we analyze the advantages and limitations of inhalation anesthesia in comparison with intravenous anesthesia in both adult and pediatric populations. The aim of the review is to assist anesthesiologists in making an informed and objective choice between the 2 techniques, considering that a single aspect—environmental pollution—although important, cannot be the only parameter on which to base the decision of how to perform general anesthesia.

Keywords

Inhalational anesthetics; Sevoflurane; Desflurane; Propofol; Total intravenous anesthesia; Pharmacokinetics of inhalational anesthetics; General anesthesia

1. Introduction

The discovery of anesthetics, the drugs which allow patients to undergo surgery without pain, movement, and memory of the surgical experience, represents a milestone in the history of medicine. Initially, anesthetic drugs were represented only by inhalational anesthetics: the inhalation route was the only route possible due to the lack of venous access, intravenous fluids, and sterile devices such as needles.

Several molecules have been developed since the original demonstration of the efficacy of ether, and nowadays the opportunity to use safe and potent inhalational anesthetics, as well as being able to measure their precise end tidal concentration at each tidal volume, explain part of their great success and diffusion.

Total Intravenous Anesthesia (TIVA) appeared later in the history of anesthesia, with the modern Target-Controlled Infusion (TCI) technique developed in the late 1990s. TIVA is currently attracting considerable interest because it is believed to have a lower negative impact on the environment than Inhalation Anesthesia (IA). Therefore, the debate over the merits of one form of anesthesia over another is now a hotly-contested topic, featured in many anesthesia journals, with conflicting opinions [1–3].

This narrative review aims at examining some characteristics that distinguish IA from TIVA, with the goal of offering an objective perspective that can help anesthesiologists choose the best way to carry out a general anesthesia (GA) for each patient and in each individual situation, both in the adult and pediatric populations.

2. Advantages of modern inhalational agents (isoflurane, sevoflurane, desflurane)

According to recent surveys, the use of inhalational agents (usually after an intravenous induction, and in association with opioids during maintenance) still represents the most common strategy to carry out GA worldwide [4]. The advantageous characteristics of volatile, inhalational agents that justify their wide use are summarized in Table 1.

In contrast to drugs used for TIVA, each modern volatile agent can provide all the classical components of GA — including amnesia, unconsciousness, muscle relaxation, and antinociception—by itself [5]. Therefore, it is possible to conduct a "pure" inhalational GA, even though today it is common to associate volatile anesthetics with other drugs (which include opioids and muscle relaxants when needed, the so called "balanced anesthesia"). Moreover, inhalational agents are effective in all patients, with only minimal reported genetic variances in potency, and no reported allergy.

A very peculiar and intriguing aspect that should be considered an advantage of inhalational anesthetics in comparison with intravenous drugs (especially propofol) is related to their pharmacokinetics (PK). Looking at the classic concentration-effect curves that characterize MAC (the minimum alveolar concentration required to prevent movement in response to a standard surgical stimulus in 50% of patients) and its

TABLE 1. Advantages of modern inhalational anesthetics.

Each single molecule reproduces all the clinical end-points of GA
Efficacy on all patients
Low pharmacokinetic variability in adult population (obese included)
Continuous measurement of their concentration in the expiratory tidal volume
No need for processed EEG monitoring to avoid awareness
Possibility of inducing GA in frail, uncooperative patients and in children when iv access not available
Low systemic toxicity: the currently used agents are minimally metabolized and are eliminated via the lungs, making them well-suited even for patients with hepatic or renal dysfunction
Bronchodilator effect; possible lung protective effect
Possible lower cost of IA *vs.* TIVA (Not for Xenon which does not pollute but costs too much to be distilled from atmosphere)
No allergies
Alternative to IV agents in case of shortage
Opioid sparing effect

GA: general anesthesia; EEG: electroencephalogram; TIVA: total intravenous anesthesia; IA: inhalation anesthesia; IV: intravenous.

derivatives, it appears that these curves have a steep slope that is consistent with little variability of the parameter within a population. Eger *et al.* [6] showed that the Standard Deviation (SD) of MAC is around 10%; therefore, according to the properties of a normal distribution, at 1.1 MAC (that is MAC + 1 SD) movement in response to a standard stimulus is prevented in roughly 68% of the population, at 1.2 MAC in 95% of patients and at 1.3 MAC in 99.7% of patients. MAC is the specific point, the median, on the dose-response curve that is equivalent to the concentration producing 50% of the maximum response (EC_{50}) for propofol. Administration of 1.3 times the EC_{50} of propofol will be effective in only 75% of patients (*vs.* 99.7% of inhalational agents), due to the well-known variability in propofol PK, and therefore in the dose requirements between individuals, to achieve the same clinical endpoint [7, 8]; the reasons for this variability are still under investigation.

A fundamental clinical target to be achieved during GA is unconsciousness. MAC-awake, the minimum alveolar anesthetic concentration needed to suppress a voluntary response to verbal command (considered equivalent to the suspension of consciousness) in 50% of patients—was introduced by Stoelting in 1970 [9]. Since MAC-awake is generally 0.3–0.5 of MAC, and considering an SD of about 10%, when 0.7–0.8 MAC is administered to patients, we are almost confident to abolish consciousness in nearly 100% of patients [10]. In modern anesthesia working stations we have the opportunity to have continuous, real-time measurement of volatile anesthetic end-tidal partial pressure as a fraction of minimum alveolar concentration (fMAC) or age-adjusted fMAC [10]. The concentration we obtain is a real measure and not a predicted value, as occurs with TIVA, no matter how the PK model of the distribution and elimination of propofol—or of other intravenous agents—might be calculated. Moreover, the ratio of MAC-awake to MAC remains the same as age increases, indicating a similar decrease with age of both MACs [11]; this parallel trend excludes the influence on MAC-awake of one of the main factors affecting MAC: age. The age-adjusted continuous measurement of volatile anesthetics concentration (and therefore of MAC) at each respiratory act is a kind of monitoring which is part of every modern anesthesia working station, without additional costs, and offers anesthesiologists the confidence to be able to prevent awareness in every patient, even in the absence of a processed electroencephalogram (pEEG) [7, 8]. Conversely, the considerable variability in the dose of propofol required to achieve the same clinical effect in different patients [12], suggests the necessary use of pEEG to carry out GA without the risk of awareness. Sometimes, not even this precaution—the use of pEEG—is sufficient to prevent awareness. Indeed, 5th National Audit Project (NAP5) reported that many cases of awareness occurred during TIVA, especially with the use of non-Target Controlled Infusion (TCI) techniques (manual infusions, fixed rates techniques, intermittent boluses) and in the absence of anesthesia depth monitoring [13].

Other advantages offered by volatile agents include the possibility of inducing GA when an intravenous access is not available, a potential lower cost, their minimal/absent metabolism which guarantees their elimination despite organ dysfunction, together with the possibility that, as happened during the COVID-19 pandemia, there may be shortage of some medications (such as propofol, or neuromuscular blocking agents), and in this case it is important to be able to use all available anesthetic techniques.

Finally, some authors have shown an organ protective effect for inhaled anesthetics, in conditions such as during ischemia-reperfusion, and a possible protective effect on microcirculation, in particular by acting on its glycocalix component [14]. However, definitive, evidence-based conclusions on this topic, based on randomized controlled trials, have not been produced yet.

Propofol as well has shown organ protection, mainly neuroprotection, in different preclinical models [15, 16], but, again, the clinical translation of these protective effects has not been

documented. Interestingly, in a meta-analysis of randomized clinical trials that aimed to evaluate whether propofol reduced survival compared to any other hypnotic agent on more than 30,000 patients, its use was associated with a trend in increased (10%) mortality [17]. Several mechanisms have been proposed for propofol's negative effect on survival [18]. However, this negative effect on survival must be confirmed in large, pragmatic, multicentric, randomized controlled trials which can exclude potential confounders.

3. Negative effects/controversial aspects of IA

There are undoubtedly negative aspects linked to the use of inhalational anesthetics, some of which severe, although rare, such as Malignant Hyperthermia, some in part preventable/treatable with other drugs, such as postoperative nausea and vomiting (PONV) (see Table 2 for a complete list). However, at present, the main negative aspect that causes concerns about IA is related to its effect on the environment. Only the effects of IA on patients' outcome will be analyzed in this paragraph, as entering into the debate on the quantitative impact of anesthesia on "greenhouse gas", or how to correctly assess the polluting effects of single volatile anesthetics [19], or how an anesthesiologist's actions, for example avoiding nitrous oxide or desflurane rather than completely abandoning all forms of IA in favor of TIVA, is not the purpose of this narrative review.

TABLE 2. Documented negative effects of inhalational anesthetics.

Side effects/risks
Increased risk of Emergence Delirium
Pulmonary complications, postoperative nausea, vomiting
Trigger for Malignant Hyperthermia
Not available/difficult to use in remote location/for patients' transport
Environmental pollution/toxic effects on workers
Interference with neuromonitoring

A negative effect of inhalational agents on the outcome of cancer patients has been speculated, due to their effect on immune system function, which may favor recurrence of cancer. There is now robust evidence indicating that anesthesia techniques, including both IA and TIVA, have a neutral effect on cancer outcome [20].

Another point of debate has been represented by the possible nephrotoxic action exerted by sevoflurane when used for long periods and/or with fresh gas flow less than 2 L/min. Again, a recent systematic review and meta-analysis of randomized controlled trials showed that there is no association between the use of sevoflurane and postoperative renal impairment compared with other agents used for anesthesia maintenance (inhalational or intravenous), even when sevoflurane is used in low flow fresh gas flow modality (less than 0.5 L/min) [21]. This is an important point, as one suggested approach to reduce pollution due to IA is to reduce fresh gas flow, and this can be done without exposing patients to the risk of compromising their renal function.

Concerning cardiac surgery, it has been shown that IA may exert a neutral effect [22, 23], or it may even offer advantages to TIVA—including reduced mortality, fewer pulmonary and other complications [24] or, finally, it may have a protective effect on mortality at 1 year [25]. A recent systematic review and meta-analysis comprising more than 51,000 patients undergoing several types of surgery indicated that postoperative mortality (30-day and 1-year mortality) and organ-related morbidity were similar for TIVA and IA [26]. TIVA, however, offered some advantages in postoperative recovery, in terms of lower incidence of PONV, Emergence Delirium (ED) and a higher quality of recovery score [26]. While the protective effect of TIVA on PONV has been consistently showed in many studies, and a protective effect seems also to be confirmed for the development of ED in elderly patients (>65 years), its role in preventing Post Operative Cognitive Dysfunction (POCD), in comparison with IA at present cannot be confirmed, due to the lack of standardized cognitive assessments, internationally-accepted diagnostic criteria and variability in timing assessment of POCD in the different studies [27].

4. TIVA versus IA in the pediatric patient: practical reflections

In the context of pediatric anesthesia, the choice between TIVA and balanced anesthesia represents a very delicate decision, where pharmacological, technical, logistical, and personal considerations converge. Both strategies are widely used in daily clinical practice, yet the practical implications of their application on children require a careful and contextualized analysis.

Balanced anesthesia, typically based on the administration of the volatile sevoflurane in combination with opioids and other adjuvant drugs, remains the gold standard in most pediatric settings due to its ease of use, rapid induction and recovery, and the possibility of continuously monitoring end tidal alveolar concentrations (therefore giving fMAC). However, the practice of IA presents some critical issues, including a higher incidence of PONV, ED, and potential neurotoxicity in neonatal and pre-school age groups, although there is now almost unanimous consensus that medium-short duration exposures to sevoflurane do not cause neurodevelopmental neurotoxicity [28–30]. The potential advantage of IA in facilitating tracheal intubation without performing neuromuscular blockade seems to have less importance today, because in both adults and children muscle paralysis is now recommended to optimize tracheal intubating conditions [31, 32]. Conversely, an undoubted and persistent advantage of choosing inhalational agents is the possibility of using them for induction of GA. Inhalational induction, a technique that may expose patients to a greater risk of complications, is indeed unavoidable in order to establish venous access in cases where this maneuver is difficult and when it is not possible or is contraindicated to administer pre-anesthesia sedation. In these cases, induction is obviously possible only with IA, which

sometimes includes the administration of nitrous oxide [33].

TIVA, particularly when using the propofol-remifentanil combination, offers several theoretical and practical advantages: better control of hypnotic depth (if adequately monitored), reduced incidence of PONV, ED and, according to some authors, reduced post-operative pain [28]. A better recovery and, in some contexts, a more stable intra-operative hemodynamic profile have also been reported [34–36]. However, the greater effort required for its safe administration should not be underestimated: the need for stable venous access, reliable infusion systems and specific training to adequately titrate the drugs cannot be overlooked.

In pediatric patients, the choice between TIVA and IA must not ignore several key variables: age, weight, type and expected duration of the procedure, presence of pre-existing neurological disorders, risk of PONV, availability of advanced anesthesia depth monitoring and, finally, availability of dedicated, specific infusion pumps (better TCI). In many cases, TIVA may be an excellent option for children at increased risk of PONV, in patients with a history of emergence agitation, or where exposure to volatile agents is to be avoided for clinical or cultural reasons [34]. Moreover, although further evidence is needed, a recent pilot study has shown that even minimal concentrations of sevoflurane TIVA with propofol attenuated the amplitudes of motor-evoked potentials in the lower limbs; to date it is therefore preferable to avoid IA in contexts requiring intraoperative neurophysiological monitoring [37]. It is, however, essential to emphasize that in younger children, particularly those under 2 years of age, TIVA requires extreme caution due to the lack of reliable biomarkers for effective drug concentration, the enormous PK variability in this population, the reduced reliability of anesthesia depth monitoring systems. Finally, the potential development of Propofol Infusion Syndrome, an event that is rare and mainly limited to settings of prolonged sedation such as the Pediatric Intensive Care Unit [38].

The anesthesiologist's experience plays a crucial role. Where there is established familiarity with TIVA and adequate technical resources are available this technique can be used safely for pediatric patients. However, routine use of TIVA in all age groups, without solid specific training, may increase the risk of overdose, delayed recovery or hemodynamic instability. Therefore, balanced inhalational anesthesia is not an inferior solution, but a technique with a high safety profile when performed correctly, particularly in settings where speed, predictability and constant monitoring of gas concentrations play a key role. Table 3 summarizes the main characteristics of the 2 techniques in the pediatric population.

5. Conclusions

There is heated debate about TIVA and IA, and the 2 methods of administering GA are often presented today as two opposing techniques between which an irreconcilable choice must be made. A growing school of thought suggests abandoning IA altogether in favor of TIVA due to the advantage the latter offers in terms of lower (but not zero) environmental pollution; the question of whether this is sufficient reason to abandon IA is legitimate. However, the relative contribution to pollution of anesthesia must be considered in relation to many other

TABLE 3. Comparison between inhalational (balanced) anesthesia and TIVA in clinical practice in the pediatric population.

	Balanced anesthesia	TIVA (Propofol–Remifentanil)
Induction	Rapid with Sevoflurane Necessary in case of absence of venous access	Stable intravenous access needed Rapid onset Effect not depending on ventilation
Depth of anesthesia	Reliable monitoring of MAC due to continuous, real-time volatile anesthetic end-tidal partial pressure	Monitoring of anesthesia depth necessary (EEG-based) Great pharmacokinetic variability in small children
Emergence	Rapid Higher incidence of ED and PONV	Smooth emergence Lower incidence of ED and PONV
Indications	Gold Standard in routine practice Short procedures Need for predictability	Malignant Hyperthermia risk Duchenne dystrophy Neurosurgery Neurophysiologic monitoring High risk of PONV/ED
Safety	High	Specific technical knowledge—Hemodynamic instability when TIVA not correctly titrated
Logistic	Easy to use in the operating room No need for special infusion devices	Dedicated specific infusion pumps (better TCI) Stable intravenous access needed—Specific training required
Environmental impact	High (especially with N_2O)	Low, but not absent (plastic waste and unused propofol)
Costs	Independent of patients' weight	Proportional to patients' weight

ED: emergence delirium; EEG: electroencephalogram; MAC: minimum alveolar concentration; PONV: postoperative nausea and vomiting; TCI: target controlled infusion; N_2O: Nitrous Oxide; TIVA: Total Intravenous Anesthesia.

aspects of healthcare that are dangerous for the environment. Moreover, the clinical evidence available does not show the superiority of one technique to the other when major outcomes are considered, and the supposed beneficial effect of TIVA in specific contexts, such as patients undergoing cancer surgery, has been excluded. There are some features of IA that we have summarized in this review that are unquestionably advantageous for patients and for administering safe anesthesia, especially in some contexts.

We suggest, therefore, that anesthesiologists should be confident with both types of anesthesia techniques, aware that the consequences of our work on the environment are not limited to the use of one group of molecules rather than the other, but include a global perspective (re-use, recycling, use of low fresh gas flow, appropriate surgical indication, and so on). Patients' safety must be a priority, according to the available devices and the context in which we operate.

The discussion between TIVA and balanced inhalation anesthesia in children is even more abstract and distant from everyday clinical practice. Rather than a dichotomous choice, it is an integrated decision-making process that must consider the characteristics of the patient, the type of surgery and the operating context. A modern pediatric anesthesiologist must have a thorough knowledge of both techniques in order to apply them selectively and individually, with the common goal of ensuring safety, efficacy and perioperative comfort.

Therefore, our opinion is that it is prudent not to abandon IA in favor of TIVA but to maintain expertise in both techniques and choose according to a patient's and a clinical context.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

CA—wrote the section on adults. AS—wrote the section on children. EGB—writing review and editing. GL—writing review and editing, supervision. All authors reviewed the text, read and approved the final manuscript. All authors conceived the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

Giovanni Landoni has lectured and been part of an advisory board for Baxter. Giovanni Landoni is serving as Editor-in-Chief of Signa Vitae. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to VL. The other authors declare no conflict of interest.

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