**Pro–Con Debate**

**Inhalational anesthesia vs total intravenous anesthesia (TIVA) for pediatric anesthesia**

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**Introduction**

Despite extensive research and development within the specialty, inhalation anesthesia remains by far the most commonly used technique in pediatric anesthesia. Volatile agents have their drawbacks, but until quite recently, techniques such as total i.v. anesthesia remained largely in the research domain. The advent of improved drugs, better understanding of pharmacokinetic/pharmacodynamic interaction, and simpler, age specific delivery systems are beginning to challenge the dominance of inhalation techniques in specific situations. Whether the benefits of total intravenous anesthesia (TIVA) can be harnessed and developed further to become the routine technique of choice in the future remains to be seen. In this paper, we objectively examine the arguments for and against inhalation and TIVA and look at where both techniques could be better adapted in the pediatric population.

**Inhalational anesthesia in pediatrics (by Jerrold Lerman)**

Millions of anesthetics are delivered worldwide to children daily. One commonality amongst these anesthetic practices is that independent of the city or country, almost all include provision for inhalational anesthesia. Whether used for induction or maintenance of anesthesia, inhalational anesthetics are pervasive because they are effective, reliable, safe, easy to deliver, stable, and without major end-organ sequelae. Five inhalational anesthetics are available for use today in children: sevoflurane, isoflurane, desflurane, halothane, and nitrous oxide. For this debate, halothane is considered of historical interest. In contrast, fewer TIVA agents are available to induce anesthesia in children (propofol and ketamine) and only one is commonly used to maintain anesthesia (propofol). In this debate, I argue in favor of inhalational anesthetics and their continued use in pediatric anesthesia.

**Key points supporting inhaled anesthesia**

- Each inhalational anesthetic satisfies the four pillars of anesthesia.
- Induction is easy without i.v. access.
- Induction of anesthesia is quick, simple and pain-free by mask.
- Easy to estimate blood tension of inhalational anesthetics noninvasively.
- Intravenous agents demonstrate excessive inter-individual variability and cannot be estimated.

**Pharmacology**

The four pillars of general anesthesia are loss of consciousness/amnesia, analgesia, ablation or blunting of autonomic reflex responses, and muscle relaxation. Potent inhalational anesthetics satisfy all four pillars to varying degrees. They induce loss of consciousness (with limited response to pain), confer amnesia, blunt reflex responses, and potentiate muscle relaxants. In contrast, single agents of TIVA such as propofol induce anesthesia, may cause amnesia, partially blunt autonomic reflex responses and do not potentiate muscle relaxants. Thus, each...
of the potent inhalational anesthetics satisfies the four pillars of a complete anesthetic, whereas TIVA techniques require mixtures of different drugs with different pharmacokinetics and pharmacodynamics to ensure a complete anesthetic.

Mechanistically, the delivery of inhalational anesthetics to the lungs provides an extremely rapid delivery of drug to the brain. Using the overpressure technique for soluble agents or the target inspired concentration for insoluble agents, the washin of anesthetics to the alveoli and thus the brain (via the arterial circulation) is particularly rapid in infants and children. In contrast, the TIVA agents are delivered through an i.v. route and are diluted in the venous circulation before passing through the heart to reach the brain and other vessel rich groups. Several layers of safety measures are incorporated into the monitoring systems to verify the delivery of inhalational anesthetics including maximum deliverable concentrations from the vaporizer and breath-by-breath measurement of the inspired and expired inhalational concentrations, which are not commercially available for i.v. drugs. Maximum and minimum concentrations for each anesthetic may be programmed into the monitor to ensure an adequate dose of anesthetic is delivered. Even when an agent analyzer is not available, measuring the oxygen and carbon dioxide concentrations in the breathing circuit confirms the integrity of the circuit. Hence, these redundant monitoring strategies provide a safety net that alarms when the inhalational anesthetic concentrations are outside the accepted range. In contrast, there is no similar safety net for TIVA. There is no mechanism to detect a disconnect in the i.v. line (1) or s.c. infiltration of TIVA before awareness occurs during surgery in the paralyzed child or if movement occurs in the nonparalyzed child. This is particularly troublesome in children as the arms are frequently tucked under the drapes thus concealing the i.v. site. There are no alarms that sound during TIVA when either excessive or inadequate doses are administered.

The depth of anesthesia can be quantified during inhalational anesthesia by measuring the endtidal partial pressure of the anesthetic (using agent analyzers), an indirect measure of the brain partial pressure of the anesthetic and by using a depth of anesthesia monitor. Steady-state measures of potency, the minimum alveolar concentration (MAC), have been determined for all inhalational anesthetics and in infants and children (2–4). Agent analyzers are present in virtually every location where inhalational anesthetics are administered. Hence, a child’s individual depth of anesthesia can be measured during every anesthetic without additional costs, even during interventions [i.e., skin incision, laryngeal mask airway (LMA) insertion]. As well, we can determine the dose to attenuate adrenergic responses and awareness. In contrast, similar measurements for the TIVA drugs are not available. There is no MAC for TIVA drugs, no measure of the MAC-multiples of TIVA that confers amnesia and no measure of the equivalent MAC-multiples to confer general anesthesia in children of different age groups.

The second method to assess the depth of anesthesia is the depth of anesthesia monitor of which there are several. In the case of the bispectral index monitor (BIS) (Aspect Medical Systems, Norwood, MA, USA), the algorithm was developed from adult electroencephalogram (EEG) patterns and with anesthetics other than sevoflurane. These monitors may not be reliable in children <5 years of age (5). When applied to children anesthetized with sevoflurane, the BIS failed to predict movement, showed large inter-individual variability and the reading actually increased at concentrations between 3% and 4% (6,7). To assess the depth of anesthesia during TIVA, <30% of the BIS reading was explained by the estimated propofol concentration (8). This left an unexplained variability in the BIS of 70% and more uncertainty about the significance of the reading than certainty. In summary, agent analyzers can estimate the depth of anesthesia during inhalational anesthesia but in the case of TIVA, there is no reliable measure.

Awareness during anesthesia in children piqued readers’ interest lately after publication of several occurrences. For the most part, these reports can be explained by lapses in an appreciation of the pharmacology of sevoflurane. Sevoflurane’s limited solubility reduces its potency. As a consequence, recovery from anesthesia is rapid whether it occurs when a child is briefly disconnected from the circuit during transport or when the child is painfully stimulated soon after induction or after the anesthetic concentrations were reduced. Failure to supplement the anesthetic or to wait for an adequate depth of

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anesthesia, may prompt similar occurrences. Although many suggest a depth of anesthesia monitor would mitigate such events, these monitors do not function properly (see above) in young children and during sevoflurane anesthesia. A recent study in adults suggested that 0.7 MAC yields a similar incidence of awareness as a depth of anesthesia monitor (9). Hence, monitoring the concentrations of inhalational anesthetics (which are accessible in every operating room) should provide sufficient monitoring to prevent recall during inhalational anesthesia when an adequate depth of anesthesia is provided, whereas during TIVA, a supplemental depth of anesthesia monitor is required, particularly because awareness may occur twice as frequently as during inhalational anesthesia (10).

In the case of TIVA, an infusion pump or a programmable device may be used to deliver a dose based on an algorithm, although the actual blood and brain concentrations of propofol (or any other drug) cannot be accurately measured in real time or noninvasively for real-time feedback as in the case of inhalational anesthetics. Dosing regimens for propofol are variable in children, with very large inter-individual blood concentrations of propofol, three- to fivefold greater than for inhalational anesthetics (4,11). Although we can administer a specific dose of an i.v. drug to a child, we are unable to measure its blood or brain concentration noninvasively.

Inhalational anesthetics are delivered by TEC vaporizers that have no moving parts and require no external source of energy, with the exception of the desflurane vaporizer. In contrast, TIVA requires multiple infusion pumps that all require external sources of energy, increasing their vulnerability to failure because of a lack of an energy source. The delivery of inhaled anesthetics is routinely monitored using commercially available noninvasive anesthetic gas analyzers. If the endtidal (child) anesthetic partial pressure or the anesthetic concentration in the circuit suddenly decreases, an alarm will sound. No such monitoring system is available for TIVA. In fact, when target controlled TIVA devices are used, the only means to determine whether the target concentration has been achieved is by invasive blood sampling.

The potent inhalational anesthetics halothane and sevoflurane have dominated anesthetic inductions in children for decades providing smooth induction of anesthesia with excellent outcomes. My usual personal practice is to induce anesthesia with the child seated on the operating table breathing 70% nitrous oxide through a scented facemask until consciousness is lost. Distraction techniques such as asking them to imagine their favorite flavor in the mask can be surprisingly effective (12). Once the child ceases to respond verbally, I introduce 8% sevoflurane in a single turn of the vaporizer dial. This speeds the induction and eliminates the risks of excitement and movement. By pretreating with 70% nitrous oxide, the child does not associate the mask with the odor of sevoflurane. I.v. access is then established after loss of consciousness, although the airway may be lost before access is secured. If laryngospasm occurs before access is secured, propofol, atropine and succinylcholine may be given by any number of routes successfully: intramuscularly, intravenously, or sublingually.

A single breath induction of anesthesia is also possible with inhalational anesthetics, resulting in induction times that are not dissimilar from those of i.v. anesthesia (13,14). After priming the anesthetic circuit with inhalational anesthetic (± nitrous oxide), the child (usually ≥5 years) exhales to residual volume and then inspires a single vital capacity breath of 8% sevoflurane and holds it. Anesthesia can be induced within 20–40 s, similar to the time required for an i.v. induction.

In the case of TIVA, i.v. access must be established before i.v. drugs can be administered. If EMLA is used, this takes up to 1 h to prepare the skin for the i.v. In many practices, the children are not present in the preoperative holding area in sufficient time to allow EMLA to be fully effective. EMLA not only topicalizes the skin, but it blanches the skin leading to venoconstriction and difficulty visualizing the veins in the hand. Ametop® (Smith & Nephew Inc., St. Laurent, Quebec, Canada), which anesthetizes the skin more rapidly than EMLA and causes no venoconstriction, is available in Europe and Canada but not in the US. Despite reassurances that these and other techniques permit a ‘pain-free’ i.v. insertion, most children around the world fear the dreaded ‘i.v.’. To circumvent this fear, anesthesia is commonly induced by mask. Once an adequate depth of anesthesia has been achieved, i.v. access can be secured.

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Intravenous induction of anesthesia with propofol is rapid, although it causes pain, apnea and occasionally hypotension in children. I.v. access is usually secured preoperatively in the dorsum of the hand, a site that is associated with much more pain after propofol and rocuronium than the antecubital fossa. Avoiding the antecubital fossa for i.v. access has been common practice for many years in children as some drugs (i.e., thiopental whose pH is very alkaline) are known to induce acute vasoospasm when injected into an aberrant (and small) artery. A number of strategies have been used to attenuate the pain of propofol administration with varied and limited success. In contrast, a gentle inhalational induction causes no pain. One extremely effective method to eliminate the pain of propofol injection in children is to pretreat the child with nitrous oxide, an anesthetic gas (15). In this case, inhalational anesthesia is used to reliably eliminate a problem created by TIVA.

Apnea may occur after a sevoflurane induction, particularly if a large concentration is administered after a midazolam premedication. Manual ventilation for a brief period and if necessary, reducing the inspired sevoflurane concentration, are usually all that is required to maintain anesthesia and facilitate return of spontaneous respiration.

Once the airway is established, any one of several inhalational anesthetics may be used for maintenance. The current ether anesthetics have limited cardiorespiratory depression, no neurotoxicity and minimal risk for hepatorenal toxicity. Spontaneous respiration is easy to maintain with an inhalational anesthetic; the decrease in tidal volume is offset by an increase in respiratory rate. Ether anesthetics depress the circulation in a dose-dependent manner that is easily reversible by decreasing the anesthetic concentration, and/or administering atropine and fluids. Isolated reports of hepatitis associated with the use of ether anesthetics have appeared in the literature, but their incidence is too small to present a substantive risk, even after repeated anesthetics.

Prolonged inhalational anesthesia has been shown to be safe. Even up to 30 days of isoflurane anesthesia yielded no toxicity (16). In contrast, prolonged administration of propofol has resulted in severe life threatening side-effects and death associated with rhabdomyolysis, lactic acidosis, myocardial toxicity and malignant dysrhythmias (propofol infusion syndrome; PRIS). This unpredictable and potentially lethal complication of propofol resulted in the issuance of a proscription of the use of propofol for prolonged sedation in children. Dexmedetomidine is not a complete general anesthetic, ketamine accumulates when given for prolonged periods resulting in delayed recovery and remifentanil is not an anesthetic. Thus, prolonged anesthesia is not amenable to TIVA.

Although the degradation of ether anesthetics has attracted much attention, the risk in children is trivial compared with that of PRIS, a potentially fatal complication that was first reported in children and that was entirely attributable to TIVA (propofol). In vivo metabolism of the ether anesthetics is most pronounced during sevoflurane anesthesia, for which inorganic fluoride has been a concern. However, the inorganic fluoride that results from in vivo degradation of sevoflurane does not cause high output renal failure because the affinity of renal CYP450 2E1 for sevoflurane is fivefold less than for methoxyflurane (17). Degradation of ether anesthetics in the CO₂ absorber, has yielded two potentially toxic products: compound A and carbon monoxide. The former results from sevoflurane degradation at low flows and the latter from isoflurane and desflurane degradation in desiccated CO₂ absorbent. Compound A has never been shown to be toxic in humans and is not considered a substantive risk (18). Carbon monoxide may be produced if isoflurane or desflurane is circulated through an absorbent containing desiccated absorbent. Absorbent becomes desiccated if several failsafe measures are disregarded: (i) the fresh gas remains flowing at a large rate; (ii) the gas continues uninterrupted for a prolonged period (~48 h); (iii) the reservoir bag is not present on the anesthetic circuit; and (iv) the inspiratory gas enters the absorbent canister, not downstream of the inspiratory one-way valve. If all of these conditions are satisfied, the absorbent may become desiccated and theoretically produce carbon monoxide when isoflurane or desflurane are introduced. To address this potential problem, several absorbents (i.e., Amsorb plus® (Armstrong Medical Inc., Coleraine, Northern Ireland), Superia, and Loflosorb®; From Intersurgical, Wokingham, UK) that produce neither compound A nor carbon monoxide, even when desiccated, have been developed (19). Finally, degradation of sevoflurane in the presence of desiccated
baralyme has produced combustible compounds that ignited a CO₂ canister (20). Subsequently, baralyme was withdrawn from the market. Hence, neither the metabolism nor the degradation of inhalational anesthetics presents substantive toxic risks to humans.

Recovery after inhalational anesthetics depends solely on exhaling the anesthetic; metabolism of the ether anesthetics does not contribute significantly to their elimination. Indeed, the context-sensitive half-life of desflurane is very small and independent of the duration of anesthesia suggesting the recovery after desflurane is both rapid and predictable (21). In fact, the blood and tissue solubilities of all ether anesthetics are small, lending themselves to a label of ‘forgiving’ as recovery after their use is rapid. Furthermore, the endtidal anesthetic gas monitoring permits a breath-by-breath progress of the speed of recovery after discontinuing these anesthetics; i.e., MAC awake for inhalational anesthetics (22) or MAC for tracheal extubation (23) have been determined. In contrast, recovery after TIVA depends on redistribution and hepatic degradation of the drugs (24), the latter being much slower than exhalation of inhaled anesthetics and in some children and in the presence of some disease states (morbid obesity), may be markedly impaired. In the case of propofol, the greater the duration of administration, the greater the recovery time as its pharmacokinetics transform from a rapid recovery paradigm to one that is much slower (25). Dexmedetomidine has been shown to have a 2-h terminal elimination half-life in children (26). Only remifentanil boasts a similar very small and predictable context sensitive half-life to that of desflurane, and that is independent of the duration of administration (27), but then again, remifentanil is not an anesthetic. Hence, recovery after brief anesthesia with TIVA may be as rapid as that after inhalational anesthetics, whereas recovery after prolonged anesthesia with TIVA is likely much more protracted than that after inhalational anesthetics.

Side-effects

Movement has been reported during sevoflurane anesthesia when i.v. access was attempted (28). Two factors increase the probability of movement in response to stimulation at induction of anesthesia: early puncture of the skin and limited depth of anesthesia. The MAC multiple concentrations of sevoflurane in the first few minutes of anesthesia are substantially less than those of halothane during the same period. This exposes a weakness of sevoflurane: that for the reduced solubility in blood, the potency is also decreased. With the maximum inspired concentration of sevoflurane from commercial vaporizers limited to 8%, the speed of induction of anesthesia with sevoflurane is less than with halothane. Hence, it is imperative to maintain a large inspired concentration of sevoflurane (and continue 70% nitrous oxide) early during the induction and to be patient before establishing i.v. access.

Epileptiform EEG activity has been reported in young children during sevoflurane anesthesia, although its significance remains unclear (29). Despite reports of EEG epileptiform activity, frank movement has been exceedingly infrequent. Indeed, grand mal seizures and postictal states have not been reported (30). Evidence suggests that the risk of epileptiform activity during sevoflurane increases when it is combined with hyperventilation (31). I recommend maintaining high concentrations (8%) of sevoflurane (and nitrous oxide) as clinically tolerated during induction of anesthesia but that spontaneous (or assisted) ventilation be maintained while maintaining normal endtidal carbon dioxide tensions (PCO₂ 35–45 mmHg).

Emergence agitation (EA) has been reported after several less soluble, ether anesthetics (32,33). Although the incidence of EA has been estimated to be as great as 80% of preschool age children after sevoflurane anesthesia (34), a validated scale to quantify the incidence and to distinguish it from pain was not available until recently (35). EA is not a new phenomenon, having been first reported about four decades ago. EA after sevoflurane is a self-limited (10–20 min in duration) phenomenon that occurs in preschool age children in the recovery room. A small dose of propofol, opioid, dexmedetomidine, or clonidine may be administered to prevent EA. This time-limited, side-effect of ether anesthetics in younger toddlers appears to be more of an interesting curiosity than a substantive risk to the child or caregiver.

Postoperative nausea and vomiting occur with a background rate of about 20% after inhalational anesthesia. For emetogenic surgery (i.e., strabismus,
T&A), the incidence of vomiting is easily controlled with combination therapy of dexamethasone and a serotonin-receptor antagonist.

Cardiac arrest has been reported after TIVA in relatively healthy infants and children, a phenomenon that is exceedingly uncommon during inhalational anesthesia (see below). Propofol has been associated with cardiac arrest in children during two notable scenarios: prolonged infusions in infants and children in intensive care unit (ICU) and in neonates at induction of anesthesia. In the former case, the evidence has been sufficient to warrant a black box warning on the propofol packaging in the USA against its prolonged use for sedation. In this scenario, cardiac arrest occurred after >48 h at >4 mg·kg⁻¹·h⁻² without warning and with devastating results (36). To date, both the long-chain triglycerides and propofol have been implicated in poisoning the cardiac mitochondria and causing cardiac arrest, which explains the difficult and poor outcomes after resuscitation (37). In contrast, inhalational anesthetics have been administered for several days without untoward results in humans. A less well-known unexpected consequence of a propofol induction has been cardiac arrest in several neonates at induction of anesthesia (38). This has been reported in the literature together with one unreported case known to the author without a totally satisfactory explanation. In these cases, the dose of propofol was not excessive and the neonates have not appeared to harbor any undiagnosed congenital defects that predisposed them to such an untoward outcome. The lack of data on the use of propofol in the neonate remains worrisome and warrants further research.

Specific considerations

Inhalational anesthetics are the primary induction agents for children with normal and difficult airways, foreign body in the airway, epiglottitis, an anterior mediastinal mass and asthma. When combined with hyperventilation, inhalational anesthetics provide excellent conditions for neurosurgery. Although TIVA without a muscle relaxant may be used for some of these conditions, it is not the preferred technique.

Rapid sequence inductions have been the mainstay of i.v. anesthesia. However, there are a number of institutions in which all infants with pyloric stenosis are anesthetized by inhalational anesthesia without adverse outcomes. There are several rare conditions for which inhalational anesthetics may not be the preferred anesthetics. These include malignant hyperthermia (nitrous oxide is permitted but the ether anesthetics are absolutely contraindicated) and congenital myopathies including central core disease, Duchenne’s muscular dystrophy, Wernig–Hoffman disease and others. Regarding Duchenne’s muscular dystrophy and Wernig–Hoffman disease, rhabdomyolysis may complicate the administration of inhalational anesthetics but this remains a relative contraindication (39). In theory, induction of anesthesia in children with right to left shunts may be slower with an inhalational anesthetic compared with TIVA (40), particularly when relatively insoluble ether anesthetics are administered. Further data are warranted to establish the veracity of this theory.

With growing global concern regarding the sustainability of the ozone layer, the environmental impact of polyhalogenated anesthetics has received increased attention (41). Inhalational anesthetics are large molecules, molecular weights of 180–200, which limit their ability to reach the stratosphere. In contrast, nitrous oxide is a small molecule with a molecular weight of only 44, less than one-fourth those of the ether anesthetics that is much more likely to reach the stratosphere than the ether anesthetics. Secondly, the half-life of ether anesthetics in the stratosphere is less than 5 years whereas that of nitrous oxide is 150 years. Finally, less than 5% of the nitrous oxide that is released into the atmosphere arises from medical sources; more than 95% are byproducts of industry. As the fresh gas flows during anesthesia have been reduced, the medical contributions of ether anesthetics and to a greater extent nitrous oxide, to depleting the ozone layer have also been substantively reduced.

The costs of anesthetics can be approached in one of two ways: the cost per hour of anesthesia or the cost per kilogram body weight. In the case of inhalational anesthetics, the cost per hour depends on the depth of anesthesia (MAC and patient/surgical factors) and the fresh gas flow. MAC increases with decreasing age, although the range of MAC from infants to adults may be 50% or less. Finally, the cost of an inhaled anesthetic is independent of
the child's weight whereas in the case of TIVA, the cost depends both on the depth of anesthesia as well as on the child's weight. That is, a 100 kg child requires about five times the i.v. anesthetic compared with a 20 kg child. Such is not the case for an inhalational anesthetic (Table 1).

Summary

Inhalational anesthetics have been the cornerstone of pediatric anesthesia for more than 150 years. Although they have been very effective with an excellent safety record, they are not perfect anesthetics. Nonetheless, the current state of TIVA does not include sufficient safeguards and monitoring to supplant inhalational anesthetics to facilitate surgery in children.

Total intravenous anesthesia in pediatrics (by Martin Jöhr)

Historically, following the first ether anesthetic in 1846, inhalational anesthesia has been the dominant general anesthetic technique for humans. However, with the introduction of propofol and remifentanil into clinical practice, 20 and 10 years ago, respectively, this situation has dramatically changed: TIVA is now a very attractive alternative and has some clear-cut advantages.

Key points supporting the use of TIVA

- Improved quality of emergence from anesthesia.
- Reduced postoperative nausea and vomiting.
- Rapid onset of action independent from the alveolar ventilation.
- Can be used in peripheral locations, it is independent from airway instrumentation.
- Nonpollutant to the theatre environment.

Features favoring an inhalational technique

Induction

Without any doubt, an inhalational technique does have advantages: skilled mask induction is a key element of modern pediatric anesthesia practice; it is adapted to the children's mental state, avoids multiple traumatizing venous punctures, and compares favorably with an i.v. induction technique (42). However, this does not exclude the use of TIVA after induction: after securing venous access, i.v. maintenance can still be used with all its advantages.

Dosing and maintenance

Dosing of inhalational agents is simple: by measuring the endtidal concentrations as an estimate of the blood concentrations, the pharmacokinetic process can be followed breath by breath in each individual patient (43). In addition, there is online proof that the anesthetic is really in the body of the patient, and has not dropped to the floor. The anesthesiologist has only to consider individual pharmacodynamic differences, which, in addition, are relatively minor with inhalational agents.

While using TIVA, the anesthesiologist has to take into account pharmacokinetic and pharmacodynamic differences between individual patients. In addition, continuous safeguarding that the drugs are reaching the patient is essential; pump failure or even paravenous infusions are a continuous threat (44). Continuous scrutiny with both clinical and more objective monitoring tools are essential; in this regard, monitoring the hypnotic state by adding EEG-based monitors will probably soon become standard in pediatric anesthesia practice (45).

Dosing i.v. agents is definitively more demanding. In no way, however, should these difficulties imply that the anesthesiologist should avoid a technique which can be clearly beneficial for the patient.

Miscellaneous aspects

Inhalational anesthesia is the traditional way to anesthetize children, the technique is established and well known to all anesthesiologists; it is difficult to teach old dogs new tricks. Anesthetic vaporizers and anesthetic machines including gas analyzers are nearly universally available, whereas infusion

| Sevoflurane | Propofol |
| 1 MAC | 2 MAC | 5 mg·kg⁻¹·h⁻¹ | 10 mg·kg⁻¹·h⁻¹ |
| 20 kg | $13.00 | $26.00 | $5.00 | $10.00 |
| 100 kg | $13.00 | $26.00 | $25.00 | $50.00 |

Assuming the following: sevoflurane: 2 lpm fresh gas flow, MW 200 U, density 1.52 g·ml⁻¹, cost $0.8 ml⁻¹; propofol: $10.00/200 mg.
pumps or even target-controlled infusion (TCI) systems and EEG-based hypnotic monitoring are not. This may be the reason why, even today, only a minority of the pediatric anesthetists in the UK use TIVA (46). However, with the focus uniquely on simplicity and safety many advances in medicine would not have been possible.

Inhalational agents may have some protective properties, e.g., myocardial preconditioning (47) and organ protection (48). However, although some influence on surrogate parameters has been shown an outcome benefit could not be demonstrated even in the sickest of adult high risk cardiac patients. Therefore, these protective properties are unlikely to have clinical impact on the normal healthy child presenting for routine minor surgery.

**Particularities of TIVA in children**

**Basic pharmacology**
Propofol is added to the body by infusion into the blood stream; and it is removed from the plasma by metabolism and by distribution to peripheral compartments. Both mechanisms are highly effective in children below 5 years of age, and, compared with adults, higher infusion rates are needed to maintain the desired plasma concentrations. In contrast, in neonates and in younger infants, propofol clearance is decreased because of immaturity of the hepatic enzyme system. A large pharmacokinetic variation exists over the pediatric age spectrum (49), whereas similar (50) or only slightly higher (51) plasma levels seem to be necessary for the desired effects in children compared to adults.

In children, higher doses of propofol are required mainly because of increased distribution from plasma to peripheral compartments. Therefore, after the termination of the infusion, the plasma levels decrease slowly, and, compared with adults, the context-sensitive half-life increases more in children (21), so that rapid awakening is not a predominant feature of TIVA in children (52). On the other hand, Ke0 (the plasma–effect–site equilibration rate constant, a large Ke0 reflects a rapid transfer to the effect site and therefore correlates with a rapid onset of action) has been reported to be larger in the pediatric patient, leading to a more rapid equilibration with the effect site (53). But data are ambiguous, with reports of an increased time to peak effect in children, too (54). However, in general, at a given plasma concentration, the hypnotic effects are rapidly obtained; and much faster deepening of anesthesia is possible with propofol compared with an inhalational agent (55).

**Clinical application**
Clinically, in healthy patients older than six months, satisfactory anesthesia can be obtained by infusing propofol and co-administering opioids: a bolus dose of propofol is followed by a continuous infusion of 13 mg kg⁻¹ h⁻¹ for 10 min, then 11 mg kg⁻¹ h⁻¹ for 10 min then 9 mg kg⁻¹ h⁻¹ thereafter. Compared to manual control, computer-controlled syringe drivers allow TCI and facilitate the drug administration (56), but they are not yet widely available for children. In addition to the evaluation of the clinical signs, cerebral pharmacodynamic feedback, such as BIS, may be especially useful in this population as the predictability of plasma propofol concentrations with the classical pharmacokinetic models is limited in children (51).

Remifentanil with its short and stable context-sensitive half-time is ideally suited for TIVA. Children need markedly higher infusion rates compared to adults (57).

**Points requiring special attention.**
Injection pain has to be dealt with, e.g., by the administration of an opioid before propofol injection and by adding lidocaine to the propofol (58). The most effective method, injection of lidocaine while a tourniquet is in place, followed by propofol, is poorly tolerated by the pediatric patient (59).

Bradycardia can occasionally occur when propofol and opioids are used, this requires attention especially during squint surgery (60). The co-administration of a vagolytic agent may be worthwhile. However, these problems can easily be dealt with.

Propofol infusion syndrome is an entity defined by lactacidosis, rhabdomyolysis, and bradyarrhythmic cardiac failure (36), first described after long-term propofol infusions to children on the ICU (61). Speculatively, illustrated by a prestigious case report (62), propofol impairs fatty acid oxidation. However, PRIS has been described not only after prolonged use in the ICU but also after short-term sedation (63) and after anesthetics of 2½ and 6 h duration in children (64,65). Therefore, careful vigilance is
needed and the total dose of propofol has to be kept small. It is the author’s practice to monitor blood gases and lactate levels in prolonged cases (over 3 h) where invasive monitoring is usually in place anyway.

**Pre-eminence of TIVA**

Quiet and peaceful recovery

Modern concepts for postoperative analgesia, have changed the atmosphere in the recovery rooms; and today postoperative agitation is considered as an abnormal and frightening behavior (66). However, even in pain-free patients, postoperative agitation is common in preschool children after sevoflurane (30), desflurane (67), and isoflurane (68,69) based anesthetics. Pediatric anesthesiologists should all be familiar with strategies for the prevention and treatment of agitation; the most evident option would be, however, to avoid inhalational agents for maintenance at all, and to use propofol instead (33,70). This increases patient’s comfort, parental satisfaction, and reduces the recovery room nurses’ workload.

Minimal postoperative vomiting

Vomiting is a major cause of postoperative discomfort in children and the main reason for admission after outpatient surgery (71). In addition, patients and parents consider postoperative vomiting as the most relevant outcome criteria. In infants, postoperative vomiting is a minimal problem, but it commonly occurs in children older than 2 or 3 years (72). This is reflected in scores that indicate that the age of the patient, duration of anesthesia and patient’s history are the most relevant risk factors (73).

The use of inhalational agents promotes postoperative vomiting, propofol does not (74). Propofol may have some antiemetic activities (75), even at very low doses (76). Propofol is mainly effective in preventing vomiting early after surgery (77). Avoiding inhalational agents is considered to be one of several options (78), or even the primary option (79) for preventing postoperative vomiting.

Anesthesia in remote locations

Anesthesia for MRI or CT scans and for radiotherapy can be administered most easily by using propofol. For many authorities, a TIVA technique is even considered to be the gold standard. Ease of administration, rapid recovery and the absence of side-effects are the key factors for its popularity. Airway instrumentation, anesthetic machine and scavenging system are not needed, spontaneous breathing is maintained, and a rapid recovery is assured.

**Intravenous anesthesia is the exclusive option**

A trigger-free anesthetic, avoiding inhalational agents completely and the use of TIVA, is a must for children who may be susceptible to malignant hyperthermia (80). Similarly, in children with Duchenne muscular dystrophy, apart from avoiding the use of succinylcholine, a propofol-based anesthetic may reduce the risk of rhabdomyolysis (81).

Head trauma and spinal cord surgery

Propofol reduces brain metabolism and cerebral blood flow; this allows easier control of raised intracranial pressures. Avoidance of inhalational agents is recommended by most if not all authorities under these circumstances (82).

Evoked potentials are suppressed or even abolished by inhalational agents, therefore, by using a propofol-based anesthetic, spinal cord monitoring can be more reliably performed (83).

Limited access to the airway and workplace contamination

When the administration of inhalational agents is not an option, e.g., during transtracheal jet ventilation or during cardiopulmonary bypass with no vaporizer available, TIVA remains the only option. By using TIVA there are no concerns regarding workplace contamination (84). An i.v. technique is therefore considered the method of choice for rigid or flexible bronchoscopy.

Conclusions

Despite some restrictions, TIVA combined with monitoring of the hypnotic state is a very attractive choice nowadays for a large part of routine pediatric anesthesia practice. It should be the recommended technique for tonsillectomy and squint surgery. The i.v. technique helps to keep the incidence of postoperative vomiting low and allows a peaceful and rapid recovery; this increases parental satisfaction and is a major step forward with respect to improved quality of care.

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Questions

1. From both your articles, there appear to be some significant advantages to a gas induction followed by maintenance with TIVA. Why do you think this has not become the preferred anesthetic technique for longer procedures. What needs to be done to make it more popular?

Lerman: I disagree that TIVA is becoming popular for prolonged procedures. After brief anesthesia, recovery after TIVA may be almost as rapid as desflurane, but not after prolonged procedures. Furthermore, prolonged TIVA may result in PRIS! The reason TIVA is being used more frequently in children is that MEPs for spine surgery require a hybrid of TIVA and ≤0.5 MAC inhaled anesthetic. For most prolonged surgeries, we use low flow desflurane. TIVA will not become popular if we require BIS to assure amnesia, PRIS remains a theoretical risk, the cost per kg after several hours continues to favor inhalational anesthetics over TIVA and a ‘smart’ device is not available for TIVA in children in North America. Long-term tolerance to inhalational anesthetics has only been reported in one study and that study was confounded by coincidental withdrawal from opioids and benzodiazepines precluding attribution of the ‘abstinence syndrome’ to isoflurane.

The assertion that TIVA results in a ‘clean emergence without nausea and vomiting’ may hold some merit but on balance, is not a compelling argument. There is no anesthetic, either i.v. or inhaled, with a flat context-sensitive half-life like desflurane. Secondly, while EA occurs in a minority of preschool age children and only lasts 15 min in postanesthesia care unit, resolving spontaneously in most instances, it remains an uncommon event. Thirdly, ample evidence confirms the anti-emetic effectiveness of dexamethasone and serotonin-receptor antagonists in children after most types of emetogenic surgery. This regimen results in a similar incidence of postoperative nausea and vomiting as propofol. Finally, anesthesiologists prefer to be safe and lazy as two key qualities in order of importance. Regarding the former quality, a vaporizer can deliver a predictable and reliable dose of inhaled agent to a child of any size, without subject to calculation error from drug dilution, calculation error as a result of the child’s weight or entering the wrong infusion rate as is too common with TIVA. For the latter quality, why would anesthesiologists prepare multiple infusion pumps for each and every case (when faced with up to a dozen cases per session...what a waste of time), when they can turn the dial on a vaporizer in a second and deliver a predictable and anesthetizing concentration to a child of any weight without concern.

Jöhr: TIVA is a relatively new technique which is technically more demanding, but has relevant advantages. There is always a delay until scientific knowledge has an impact on clinical practice. Most importantly, further education is needed to reduce this gap; in addition, the increased availability of infusion pumps and monitoring devices such as BISTM will undoubtedly promote a more widespread use of the TIVA technique.

2. Remifentanil appears to be preferred over alfentanil or fentanyl for the analgesic component of TIVA. Yet remifentanil cannot provide postoperative analgesia and it has been shown to produce acute tolerance and increased postoperative analgesia requirements (Guignard B et al. Anesthesiology 2000; 93: 409). My question is therefore why do you prefer remifentanil and how do you get over the issue with tolerance?

Lerman: the main preference for Remifentanil is its context-sensitive half-life. Fentanyl’s and alfentanil’s increase with duration of infusion. Vomiting postoperative is a major problem with alfentanil and it is no longer used anywhere I have been in the past 5–10 years! How to get over tolerance? There is no simple solution. Switch to another analgesic.

Jöhr: Remifentanil with its short and constant context-sensitive half-life has the optimal pharmacokinetic profile and is the ideal partner of propofol. It is preferred over alfentanil or fentanyl as the infusion rate can be kept high up close to the end, thus allowing a timely reduction of the propofol concentrations which are declining much more slowly.

Remifentanil does not provide postoperative analgesia, therefore, other options have to be chosen: regional blocks, nonsteroidal anti-inflammatory drugs (NSAIDs) and the timely administration of longer acting opioids, e.g., morphine or fentanyl. The downside of remifentanil is an increased opioid requirement in the early postoperative phase;
however, this acute tolerance can easily be dealt with by giving the necessary morphine doses. Nevertheless, the infusion rate of remifentanil should be kept as low as possible in order to minimize these problems. Anyway, awakening after propofol–remifentanil is still quiet in most cases, whereas after sevoflurane–remifentanil it is not.

3. Can commercial depth of anesthesia monitoring be used with confidence in TIVA in children and what do you rely on in your own clinical practice with TIVA or inhalation anesthesia?

Lerman: TIVA does not reliably work with the BIS in children. Moreover, sevoflurane has a different EEG profile than the methyl ethyl ether anesthetics and therefore can actually produce increasing BIS values as the sevoflurane concentration exceeds 3%. I always use N2O unless contraindicated, which is an important factor in preventing awareness. As 0.7 MAC inhalational anesthetic reduces the risk of awareness (as well as awareness monitors), then monitoring endtidal gas concentration should prevent most instances of awareness. In my practice, I always assume the child may be lightly anesthetized when performing a stimulating maneuver during the early part of anesthesia (i.e., during insertion of an LMA, tracheal tube or bronchoscope), so I administer 1–2 mg·kg\(^{-1}\) propofol i.v. prophylactically.

Jöhr: Monitoring the hypnotic state by using EEG-based devices, e.g., BISTM, is feasible in children, too. These monitors do not reflect the depth of anesthesia, as low BISTM values in the range of 10–20 also occur during natural sleep. Therefore, they are unable to predict the likelihood of movements, but they clearly indicate that the child was unconscious a couple of seconds ago. As with any monitoring device, there are several limitations: All EEG-based devices do not work for monitoring hypnosis during the first year of life, ketamine disturbs the readings, and young children tend to have higher BISTM values at what is thought to be equivalent dosing (at one MAC, age adjusted).

Although, there is still some way to go, my message today is: these devices deserve more widespread use, they are adjunct tools that measure an output derived directly from the target organ brain, which is clearly superior to only looking at surrogate parameters, such as tearing, blood pressure, or pulse rate, in order to decide if a child is awake or asleep.

4. How serious is postanesthesia agitation with sevoflurane in your clinical practice and what steps do you take to avoid this problem?

Lerman: It was a problem when sevo was introduced. The problem has dissipated for the most part over the past few years. It is a transient phenomenon, lasting 15 min or less. We first assure that analgesia is adequate. Then, we often comfort the child, but if the child does not calm down, we would administer one of a variety of medications (small single dose propofol, morphine, or midazolam).

Jöhr: Postoperative agitation is a common and clinically serious problem in children and not only an ‘interesting curiosity’. Up to 6–8 years of age, it is regularly seen in a large proportion of patients after an inhalational anesthetic, especially after sevoflurane. It occurs even in a completely pain-free child. An agitated child is a challenge for the recovery room nurses, the parents are frightened that something went wrong, and the child does definitively not seem to be comfortable or even bears the risk of self injury. Therefore, a clear concept for prevention of agitation is of paramount importance: (i) a peaceful recovery of a pain-free child by using local anesthetics and NSAIDs; (ii) opioids, clonidine, and ketamine all offer some protection against agitation and are given when needed; and (iii) in our institution, when pain is not the problem, repeated doses of thiopentone or propofol guarantee a peaceful recovery. However, the most evident option is to avoid inhalational agents in the first place.

Conclusions

Human nature is such that our choices of anesthetic technique may pivot around the security associated with familiarity, particularly in the care of children. The advent of sevoflurane has undoubtedly tipped the balance of anesthetic induction towards inhalation anesthesia even in sicker children. However, as user friendly delivery systems for TIVA become age specific with incorporated pediatric algorithms, the technique will begin to challenge the current simplicity of volatile agent delivery. There are benefits of TIVA, even perhaps in anesthetic costs (Table 1), but the issue of ensuring unconsciousness in all situations has yet to be solved. Both authors have considered the hybrid approach with inhalation induction followed by TIVA and this may be a
bridge to the future of more widespread use of TIVA in children.

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