



## Pediatric Anesthesia & Pain Management

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Total intravenous anesthesia (TIVA) in infants and children

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### Table of Contents

Table of Contents .....	1
List of Tables .....	1
Introduction .....	2
Intravenous anesthetic agents.....	2
Acquisition Cost of Anesthetic Agents.....	2
Safety.....	4
Patient Satisfaction.....	4
Applications for TIVA.....	5
TIVA: The Future .....	5
References .....	6

### List of Tables

Table 1. Hourly cost of commonly used inhalational anesthetic agents.....	3
Table 2 Hourly cost of intravenous anesthetic agents.* .....	3
Table 3. Hourly cost of inhalational and intravenous anesthetics.* .....	4

# Total Intravenous Anesthesia (TIVA) In Infants And Children

## Introduction

The use of intravenous (IV) agents to provide complete anesthesia has gained popularity in the past decade. This is due to the advent of newer drugs which have favorable pharmacokinetic (PK) and pharmacodynamic (PD) properties; an enlarging database of clinical studies incorporating these newer drugs; and innovative drug infusion devices allowing for refined dosing and targeting of plasma concentrations. Even as newer volatile agents have emerged which have more rapid onset and offset, problems with inhalational anesthesia remain. These include airway irritability during induction and emergence, rhabdomyolysis and hyperkalemia, prolonged emergence, agitation, nausea and vomiting in the postoperative period, and environmental contamination. These and other problems associated with inhalational anesthesia continue to spur the development of novel intravenous agents and techniques.

## Intravenous anesthetic agents

Rational use of IV anesthetics relies on understanding of their PK, PD, and drug interactions. Sedative/hypnotic drugs and opioids act synergistically, allowing for use of reduced doses of these agents over time, thereby diminishing adverse effects and time to emergence.<sup>1,2</sup> Therefore, TIVA techniques incorporate a combination of drugs in these two classes. Perhaps the most widely used sedative/hypnotic agent is propofol. Propofol has a rapid onset due to rapid blood-brain equilibration.<sup>3</sup> It has a relatively rapid offset, although washout from fat tissue is delayed following prolonged infusion.<sup>4</sup> Compared with adults, the volume of distribution and clearance of propofol are increased, so that higher bolus and continuous infusion doses are required. The use of target-controlled infusions of propofol have been described in adults, and dosing requirements are now being established for pediatric patients.<sup>5</sup> Propofol has antiemetic effects, resulting in a reduction in postoperative nausea and vomiting (PONV).

Remifentanil is a synthetic opioid which has many of the properties of the “ideal” IV anesthetic. Like propofol, remifentanil has a rapid blood-brain equilibration. Remifentanil undergoes ester hydrolysis to inactive metabolites in blood and tissues. Unlike other opioids, therefore, its elimination is independent of hepatic or renal clearance, resulting in highly predictable termination of its effects regardless of dosing and duration of infusion.<sup>6</sup> The context-sensitive half life of remifentanil remains about three minutes even after prolonged infusions.

The combination of propofol and remifentanil for TIVA is attractive based on their individual desirable properties and synergistic effect when used concomitantly. Propofol may also be used effectively with other opioids, including fentanyl, alfentanil, and sufentanil. The doses of propofol and opioids may be reduced when benzodiazepines, nitrous oxide, and/or regional anesthesia are used (though the latter represent a departure from “pure” TIVA).<sup>7</sup> Other agents which have been used for TIVA include etomidate, methohexital, and ketamine.

## Acquisition Cost of Anesthetic Agents

The cost of inhalational anesthetic agents varies with fresh gas flow (FGF) but is independent of the weight of the patient. The hourly cost of commonly used inhalational anesthetic agents for maintenance of anesthesia at a FGF of 3 liters/minute and 1 liter/minute are shown in Table 1.

## Total Intravenous Anesthesia (TIVA) In Infants And Children

**Table 1. Hourly cost of commonly used inhalational anesthetic agents.**

<b>Agent</b>	<b>1 MAC</b>	<b>FGF (L/min.)</b>	<b>Cost* (\$/hr.)</b>
<b>Isoflurane</b>	1.15%	3	\$2.24
		1	\$0.75
<b>Sevoflurane</b>	1.71%	3	\$13.15
		1	\$4.38
<b>Desflurane</b>	6.0%	3	\$20.15
		1	\$6.72
<b>Halothane</b>	0.77%	3	\$0.37
		1	\$0.12

\*Based on acquisition costs at Stanford University Hospital. Cost in \$/hr: (vapor conc)(FGF)(60min/hr)(molecular wt.)(cost/ml)(2412)(density)

The cost of intravenous agents varies directly with the weight of the patient, as shown in Table 2.

**Table 2 Hourly cost of intravenous anesthetic agents.\***

<b>Agent</b>	<b>Rate</b>	<b>Cost (\$/ml)</b>	<b>Cost – 70 kg (\$/hr.)</b>	<b>Cost – 15 kg (\$/hr.)</b>
<b>Propofol (10 mg/ml)</b>	150 µg/kg/min	\$0.43	\$27.09	\$5.81
<b>Fentanyl (50 µg/ml)</b>	3 µg/kg/hr	\$0.128	\$0.54	\$0.12
<b>Remifentanil (50 µg/ml)</b>	0.3 µg/kg/min	\$0.45	\$11.33	\$2.43
<b>Remifentanil/ Propofol (1:1,000)</b>	0.15 µg/kg/min 150 µg/kg/min	\$0.52	\$32.84	\$7.04

\*Assuming no drug wastage.

In pediatric patients, the cost of with intravenous anesthetics may be substantially less than in adults. Assuming no drug wastage, the cost of propofol plus remifentanil for a 15 kg child is approximately one third that of desflurane at a FGF of 3 liters/minute and about one half that of sevoflurane at a FGF of 3 liters/minute (Table 3). At a reduced FGF of 1 liter/minute the cost of these three anesthetic techniques becomes similar. Of course, drug wastage may increase the cost of intravenous agents. On the other hand, TIVA becomes even more cost-effective in infants and smaller children.

## Total Intravenous Anesthesia (TIVA) In Infants And Children

**Table 3. Hourly cost of inhalational and intravenous anesthetics.\***

<b>Agent</b>	<b>Rate</b>	<b>Cost (\$/hr.) – 15 kg</b>
<b>Desflurane</b>	1 MAC/FGF 3 L/min	\$20.15
<b>Sevoflurane</b>	1 MAC/FGF 3 L/min	\$13.15
<b>Remifentanil/ Propofol</b>	0.15 /150 µg/kg/min	\$7.04
<b>Desflurane</b>	1 MAC/FGF 1 L/min	\$6.72
<b>Propofol</b>	150 µg/kg/min	\$5.81
<b>Sevoflurane</b>	1 MAC/FGF 1 L/min	\$4.38
<b>Isoflurane/ Remifentanil</b>	0.5 MAC/FGF 1 L/min 0.3 µg/kg/min	\$2.81

\*Assuming no drug wastage.

Consideration of the cost of various anesthetic techniques must include total OR and PACU expenses. Discharge times from the PACU may be shortened when propofol is used for induction and maintenance of anesthesia compared with inhalational agents, including sevoflurane.<sup>8,9</sup> However, overall OR and PACU costs may not be decreased unless this allows ORs to run later without necessitating unplanned hospital admission.<sup>10</sup> In addition, acquisition costs of anesthetic agents represent a very small percentage of overall hospital costs.<sup>11</sup> Therefore, modest differences in these drug costs are unlikely to impact hospital costs. Several studies have shown a decreased incidence on PONV following propofol vs. inhalational anesthesia. Unless PONV results in unplanned hospital admission, however, it does not significantly increase PACU costs.

### Safety

Inhalational anesthesia is associated with a number of hazards. Many deaths have been reported due to hyperkalemic cardiac arrest in children with undiagnosed “dystrophinopathies” who are exposed to volatile anesthetic agents. Malignant hyperthermia is associated with the use of succinylcholine and volatile anesthetics in susceptible patients. Toxic compounds are produced during the use of these agents, including fluoride ion, carbon monoxide, and compound A.<sup>12,13</sup> Significant environmental contamination occurs during the use of inhalational anesthetic agents, especially during use of a facemask and uncuffed endotracheal tubes.

While allergic reactions and infection may occur secondary to the use of propofol, these are extremely uncommon and rarely, if ever, fatal.

### Patient Satisfaction

Patient satisfaction is increasingly being used by third party payers as a benchmark of quality of care. Propofol has been associated with significantly greater patient satisfaction than isoflurane in adult patients undergoing outpatient surgery. There appears to be an increased frequency of emergence delirium and disorientation with inhalational agents, with up to 55% of children crying

## Total Intravenous Anesthesia (TIVA) In Infants And Children

inconsolably, thrashing, or “hysterical” in the PACU.<sup>14,15</sup> Many anesthesiologists caring for children have noted a significant incidence of intractable screaming and agitation following the use of sevoflurane (ref). In addition, the reduction in PONV following propofol anesthesia compared with inhalational agents may account for enhanced patient (and family) satisfaction.

### Applications for TIVA

Perhaps the most popular TIVA techniques combine propofol with an opioid such as fentanyl, alfentanil, or remifentanil. In our pediatric practice at Stanford, we commonly mix propofol and remifentanil in a single syringe. For routine procedures, remifentanil 0.1 mg added to propofol 100 mg (10 ml) yields a 1:1,000 mixture. For maintenance of general anesthesia, this mixture is infused at a dose of 0.10-0.20 µg/kg/min of remifentanil and 100-200 µg/kg/min of propofol. For especially stimulating procedures, such as rigid laryngoscopy/bronchoscopy, the concentration of remifentanil is doubled (i.e. a 1:500 mixture is used). The dosage is decreased when nitrous oxide is used. Due to the synergistic effect of these agents, the dosage is also diminished gradually during procedures lasting longer than 45-60 minutes.

There are a variety of surgical procedures for which TIVA is particularly well suited. One example is rigid laryngoscopy/bronchoscopy, wherein TIVA (unlike inhalational anesthesia) facilitates the continuous administration of anesthesia with no environmental contamination. Rapid recovery occurs even with the high doses of agents required to provide adequate anesthesia for these procedures. Similarly, TIVA for craniotomies allows for increased drug dosing prior to brief periods of intense surgical stimulation as well as rapid emergence for early neurologic assessment postoperatively. TIVA for cardiac surgery may include a high-dose opioid technique (remifentanil) to minimize the stress-response to surgery while allowing tracheal extubation in the OR immediately following surgery.

In the cardiac catheterization and neurointerventional laboratory, TIVA is well suited for procedures under sedation or general endotracheal anesthesia. For the latter, we reduce the remi/propofol infusion to “sedative” doses (e.g. remifentanil 0.02 µg/kg/min and propofol 20 µg/kg/min) following tracheal extubation while pressure is maintained over femoral arteriotomy and venotomy sites. This minimizes patient movement and blood pressure elevation which may cause prolonged bleeding. The infusion may be continued during transport to the PACU.

When opioids having rapid offset (e.g. remifentanil) are used for procedures associated with postoperative pain, strategies must be employed to ensure postoperative analgesia. One approach is the use of longer acting opioids administered near or immediately following the completion of surgery. Alternatively, TIVA may be combined with local or regional anesthesia.

### TIVA: The Future

Studies are needed which clarify the PK and PD of newer intravenous agents in neonates, infants, and young children. This will facilitate the use of target-controlled infusions aimed at achieving and maintaining predetermined plasma and tissue concentrations for these drugs. Drug delivery devices which are compact and user-friendly will enhance the use of target-controlled infusions. Monitors of anesthetic depth will facilitate use of minimal doses of anesthetic agents, allowing rapid emergence and recovery.

## Total Intravenous Anesthesia (TIVA) In Infants And Children

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