An Overview about Total Intravenous Anesthesia

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Abstract

Background: Pharmacokinetics and pharmacodynamics of popular intravenous drugs like propofol and newer and shorter acting agents like remifentanil coupled with the development of pharmacokinetic models and advanced technology in infusion pumps have made a significant impact in the evolution of total intravenous anaesthesia (TIVA). Target-controlled infusion (TCI) pumps and depth of anaesthesia monitors have made TIVA easy, safe, and precise. However, TIVA can also be practised with routine infusion pumps and even when these sophisticated models of equipment are not available. TIVA may be provided either with insertion of an endotracheal tube or supraglottic airway device, nasal or oral airway, or oxygen alone without insertion of any airway device. The practice of TIVA started initially in the fields of neurosurgery, day care surgery, as a supplementation to regional or local anaesthesia, and for sedation/analgesia in diagnostic/therapeutic procedures. In recent times, it has proven to be beneficial in oncosurgery, paediatric and geriatric surgery, cardiac surgery, and non-operating room anaesthesia (NORA).

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Introduction

Pharmacokinetics and pharmacodynamics of popular intravenous drugs like propofol and newer and shorter acting agents like remifentanil coupled with the development of pharmacokinetic models and advanced technology in infusion pumps have made a significant impact in the evolution of total intravenous anaesthesia (TIVA). Target-controlled infusion (TCI) pumps and depth of anaesthesia monitors have made TIVA easy, safe, and precise. However, TIVA can also be practised with routine infusion pumps and even when these sophisticated models of equipment are not available. TIVA may be provided either with insertion of an endotracheal tube or supraglottic airway device, nasal or oral airway, or oxygen alone without insertion of any airway device. The practice of TIVA started initially in the fields of neurosurgery, day care surgery, as a supplementation to regional or local anaesthesia, and for sedation/analgesia in diagnostic/therapeutic procedures. In recent times, it has proven to be beneficial in oncosurgery, paediatric and geriatric surgery, cardiac surgery, and non-operating room anaesthesia (NORA) **(1)**.

Indications

Indications for TIVA include: **(2)**

Patients with a history of adverse reactions to inhalational anesthetics: Some individuals may have a known hypersensitivity or intolerance to volatile inhalational agents. In such cases, TIVA provides an alternative method of anesthesia that avoids the use of these agents.
Patients with compromised lung function: TIVA may be preferred in patients with pre-existing lung diseases, such as chronic obstructive pulmonary disease (COPD), asthma, or reactive airway disease. Avoiding volatile inhalational agents reduces the risk of bronchospasm and other respiratory complications.
Day surgery or outpatient procedures: TIVA is often employed for shorter surgical procedures, particularly those performed on an outpatient basis. The rapid onset and offset of intravenous anesthetics allow for a smooth recovery and early discharge of the patient.
Neurosurgical procedures: TIVA can be advantageous for neurosurgical cases where precise control of cerebral hemodynamics and intracranial pressure is crucial. Intravenous agents, such as propofol, have minimal impact on cerebral blood flow and can provide stable anesthesia in these cases.
Cardiac surgery: TIVA may be used in cardiac surgery, especially when a cardiopulmonary bypass machine is involved. Intravenous agents can be easily titrated to maintain stable hemodynamics during bypass and post-bypass periods.
Geriatric patients: Elderly patients often have reduced physiological reserve and are more susceptible to the side effects of volatile inhalational agents. TIVA allows for precise control of anesthesia and avoids the potential adverse effects on the cardiovascular and respiratory systems in this population.
Enhanced recovery after surgery (ERAS) protocols: TIVA is sometimes incorporated into ERAS protocols, which aim to optimize perioperative care and accelerate postoperative recovery. TIVA's rapid onset and offset, along with its reduced impact on postoperative nausea and vomiting, can contribute to faster patient recovery **(3)**.

Advantages of Total Intravenous Anesthesia

Advantages of Total Intravenous Anesthesia includes the following: **(4)**
Precise control of anesthesia depth: TIVA allows for meticulous titration of intravenous anesthetic agents, resulting in accurate control over the depth of anesthesia. This enables opti mal patient comfort and surgical conditions.
Smooth induction and emergence: TIVA provide a sm oother transition into and out of anesthesia compared to inhalational agents. The absence of volatile anesthetics avoids issues such as airway irritation, coughing, and emergence delirium.
Stable hemodynamics: TIVA offers stable hemodynamic control, especially in patients with compromised cardiovascular function. Intravenous anesthetics, when administered judiciously, minimize fluctuations in blood pressure and heart rate.
Reduced risk of adverse respiratory effects: By avoiding volatile inhalational agents, TIVA minimizes the risk of respiratory complications such as bronchospasm, coughing, and airway irritation. This makes it a suitable choice for patients with compromised lung function or a history of adverse reactions to inhalational agents.
Rapid onset and offset of anesthesia: Intravenous anesthetics used in TIVA, such as propofol and barbiturates, have rapid onset and offset properties. This allows for quick induction, precise titration, and a smooth recovery process, particularly important for day surgery or outpatient procedures.

Drugs/combinations in total intravenous anesthesia

An ideal drug for TIVA should have rapid onset of action, rapid recovery, be potent and lipid soluble, and be stable in solution, with no perivascular sloughing if extravasated. It should be water-soluble to minimise toxicity associated with the solvent, not be absorbed by plastic, be devoid of adverse effects, be cost -effective, and, most importantly, it should be compatible with other agents such that it can be mixed without any complication **(5)**.

Drugs/combinations in total intravenous anesthesia include: (6).

Propofol (2,6-diisopropylphenol): Propofol is a short-acting intravenous hypnotic agent commonly used for induction and maintenance of anesthesia in TIVA. It acts as a positive allosteric modulator of gamma-aminobutyric acid (GABA) receptors, resulting in sedation, hypnosis, and amnesia. Propofol has a rapid onset of action, allowing for smooth induction of anesthesia, and a relatively short duration of action, facilitating quick recovery. However, it can cause dose-dependent respiratory depression and hypotension **(7)**.

Remifentanil: Remifentanil is a potent opioid analgesic frequently used in TIVA. It is a selective mu-opioid receptor agonist with a rapid onset and ultra-short duration of action due to its rapid metabolism by nonspecific tissue and plasma esterases. Remifentanil provides effective intraoperative analgesia and can be easily titrated to achieve the desired level of pain control. It is crucial to monitor for respiratory depression, bradycardia, and potential postoperative opioid-induced hyperalgesia. Both Propofol and remifentanil remain the most appropriate and near-ideal drugs for TIVA. Remifentanil is effective in reducing propofol requirements by up to 50%. Its combination with propofol is highly effective and constitutes the most common drug combination by TCI model worldwide because of the low context-sensitive half-life. Propofol reduces the dose of remifentanil by its analgesic properties and by reducing hyperalgesia caused by remifentanil **(8)**.

Dexmedetomidine: Dexmedetomidine is a selective alpha-2 adrenergic agonist used as an adjunct in TIVA to provide sedation, anxiolysis, and analgesia. It acts by reducing sympathetic outflow, leading to sedative effects without significant respiratory depression. Dexmedetomidine has a longer duration of action compared to other sedatives and can be beneficial for procedures requiring a calm and cooperative patient. However, it may cause bradycardia and hypotension, necessitating careful monitoring.

Ketamine: Ketamine is a dissociative anesthetic that acts primarily as an N-methyl-D-aspartate (NMDA) receptor antagonist. It produces sedation, analgesia, and dissociation from the surrounding environment while maintaining cardiovascular stability. Ketamine's unique properties make it suitable for cases where hemodynamic stability is crucial or for patients with bronchospasm or reactive airway disease. However, it can induce hallucinations, emergence reactions, and increased salivation.

Midazolam: Midazolam is a short-acting benzodiazepine commonly used for its sedative, anxiolytic, and amnestic properties in TIVA. It enhances the inhibitory effects of GABA, resulting in sedation and anxiolysis. Midazolam has a rapid onset and can be titrated to achieve the desired level of sedation. However, it can cause respiratory depression, especially when used in higher doses, and may lead to prolonged sedation and delayed recovery.

Fentanyl: Fentanyl is a potent opioid analgesic used in TIVA to provide intraoperative pain control. It acts as a mu-opioid receptor agonist, producing potent analgesia and sedation. Fentanyl has a rapid onset and relatively short duration of action, making it suitable for titration during surgery.

However, it can cause respiratory depression, bradycardia, and other opioid-related side effects **(9)**.

While the search for such an ideal drug continues, TIVA is being practised with a combination of drugs to overcome the disadvantages of each. The combination of various classes of drugs and adjuncts in TIVA is necessary for complete and balanced anaesthesia. It decreases the dose of individual drugs, thereby reducing the side effects of all drugs in a mixture **(10)**.

Various adjuncts are being administered during TIVA to reduce the intra- and postoperative complications. Dexamethasone, an anti-inflammatory drug, in a single dose of 8 mg reduces postoperative nausea and vomiting by 30% in propofol-based TIVA, with good quality of recovery and discharge **(Gupta, 2017)**. Lidocaine used in a bolus dose of 1–1.5 mg/kg with infusion of 1.5 mg/kg/h reduces TIVA dose by 10%–20% during the maintenance phase. Magnesium sulphate used as an adjunct in TIVA reduces propofol, dexmedetomidine, atracurium, and postoperative narcotic consumption. Used in a bolus dose of 30–50 mg/kg with maintenance dose of 10 mg/kg/h, it improves the quality of postoperative analgesia. Its anti-hypertensive, bronchodilator, anti-arrhythmic, anti-shivering, and anti-seizure effects are an added advantage. Esmolol 1 mg/kg bolus over 60 s during preoxygenation is able to reduce the total induction dose by 18.5%. Perioperative esmolol infusion has been shown to reduce the total anaesthetic and analgesic requirements and postoperative pain **(11)**.

Table (1): Some useful IV drug combinations used for TIVA and postoperative analgesia **(6)**.

Combination of TIVA	Doses/Concentration	Clinical Applications
Remifentanil and propofol	Remifentanil in concentration of 50 µg/ml (1 mg in 20 ml propofol)	Most widely used in the world for TIVA by TCI. 50% reduction in dose of propofol is seen. Can be used for up to 36 h
Propofol and fentanyl	Propofol (1% and 2%) and fentanyl (10–50 µg/ml)	No significant degradation of emulsion within 20 h. 50% reduction is seen in dose of propofol
KPD (ketamine + propofol + dexmedetomidine)	1:1:1 initially then maintenance with 0.5:0.5:0.5 (mg: mg:µg/kg/h) Or Dexmedetomidine 0.7 µg/kg/h in RL Or Propofol 6–8 mg/kg/h in 100 ml NS	Combination of all these drugs permit lower dose of each agent and reduces adverse reactions Dexmedetomidine reduces shivering caused by propofol Excellent analgesia and anaesthesia Haemodynamically stable, rapid recovery
Ketofol (ketamine and propofol)	1:1 mixture is stable 100 mg ketamine: 100 mg propofol 0.5 mg/kg followed by another 0.5 mg/kg after about 30–60 s Maintenance 0.25 mg/kg as needed	Widely used by anaesthesiologists for short procedures
Ketodex (ketamine and dexmedetomidine)	1 µg/kg of dexmedetomidine and 1–2 mg/kg of ketamine. This could be followed by 1–2 µg/kg/h of dexmedetomidine infusion with supplemental bolus doses of 0.5–1 mg/kg of ketamine as needed	Paediatric patients for radiological and endoscopic procedures
Ketomed (ketamine and midazolam)	1 mg/kg ketamine+0.1 µg/kg midazolam	Non–operating room anaesthesia
MDF (midazolam, dexmedetomidine, and fentanyl)	0.05 mg/kg midazolam+1 µg/kg dexmedetomidine+1 µg/kg fentanyl bolus and half the previous dose if required	Widely used in COVID-19 Short surgical procedures, commonly used as adjunct
PDF (propofol, dexmedetomidine, and fentanyl)	1 mg/kg propofol+1 µg/kg dexmedetomidine+1 µg/kg fentanyl bolus and half the previous dose if required	Short surgical procedures, widely used in COVID-19
DML (dexamethasone, magnesium sulphate [$MgSO_4$], and lidocaine)	8 mg dexamethasone+1 gm $MgSO_4$+1.5 mg/kg lidocaine	Reduces postoperative nausea and vomiting, reduces doses of IV anaesthetic agents, improves quality of TIVA, recovery and discharge
FLK (fentaketacaine)	100 µg fentanyl+100 mg lidocaine+100 mg ketamine in 500 ml RL, given in dose of 0.5:0.5:0.5 (µg: mg: mg/kg/h) for maximum of 24h	Used as drip after major surgery of duration >3 h

Ketacaine drip	100 mg ketamine+100 mg lidocaine in 500 ml RL Given in dose of 0.5:0.5 (mg: mg/kg/h)	Used after routine surgery of duration <3 h
Etomidate and fentanyl/remifentanil	IV etomidate 0.3 mg/kg+IV fentanyl 1 μg/kg bolus. Maintenance with intermittent bolus etomidate 0.1 mg/kg when needed	Useful in haemodynamically unstable patient for short surgical procedures to be cautious about adrenocortical suppression; if low cortisol level/geriatric patient, dose of etomidate to be reduced to 0.2 mg/kg Pharmacokinetic model for TCI of etomidate not yet available

TIVA=Total intravenous anaesthesia, COVID=Coronavirus disease, TCI=Target-controlled infusion, IV=Intravenous, RL=Ringer lactate, NS=Normal saline.

The new addition of remimazolam in the armamentarium of TIVA is promising for procedural sedation and anaesthesia. It is pharmacologically a benzodiazepine, but is differentiated by its ester group and rapid metabolism by tissue esterases to a significantly less active metabolite. Its rapid pharmacokinetics and pharmacodynamics with relatively small effects of covariates such as age, gender, race, obesity status, American Society of Anesthesiologists (ASA) physical status, and weight will make it a perfect addition in TIVA regimens **(12)**. Another new intravenous anaesthetic is Ciprofol, it is a gamma- aminobutyric acid (GABA) receptor agonist and is a novel 2,6-disubstituted phenol derivative like propofol with improved pharmacokinetic and pharmacodynamic characteristics. It has a rapid rate of onset and recovery in preclinical experiments. It is five times more potent than propofol, does not cause pain on intravenous injection, and provides better haemodynamic stability. It is better in prolonged infusion due to rapid clearance. It can be given in initial doses of 0.4 mg/kg for 30 s followed by a supplemental intravenous bolus dose of 0.1 mg/kg for 10 s. The maintenance infusion dose is 0.1–0.3 mg/kg/hour **(13)**.

Techniques in Total Intravenous Anaesthesia

TIVA can be administered by various techniques like intermittent bolus, fixed rate or manually controlled infusion, or TCI. These techniques are heterogeneous in nature and vary significantly in their safety and efficacy. Advancements have been made in different areas along with the use of specialized infusion sets and mobile applications to make it a safe technique **(6)**.

- **Advancement in target-controlled infusion techniques**

TCI technology is constantly evolving, with innovations in drug delivery devices, pharmacokinetic modelling, and computer technology. In advanced closed-loop anaesthesia delivery system (CLADS), a controller allows a change in dose either manually or automatically based on the feedback from clinical or physiological monitors. In order to achieve precise dosing, improved haemodynamic stability, and faster recovery, reliable feedback is very important **(14)**. Advancements in TCI techniques are aimed to achieve reliable feedback either from physiological monitoring or through processed electroencephalogram (pEEG) monitoring, which have shown some promise in improved haemodynamic stability and faster recovery. Knowing the median effective effect-site concentration of the drug being used in TCI for a particular type of surgery can be useful and can guide the anaesthesiologist during drug infusion; for example, a median effective effect-site concentration of 3.38 μg/ml of propofol is required to prevent patient movement during uterine dilatation and curettage **(15)**.

Sedasys, a computer-assisted personalised sedation system, integrates continuous physiologic monitoring with patient feedback to control the depth of sedation. This technique is found to be very effective for non–operating room sedation as it intends to maintain constant sedation, thereby reducing the risk of apnoea, haemodynamic instability, and loss of responsiveness. pEEG monitoring can be used to monitor the effect of the anaesthetic drug on the cerebral cortex, thereby reducing the incidence of awareness during TIVA **(16)** . Propofol requirement can be significantly reduced by titrating the dose to a processed EEG score. It is also recommended to use this monitor whenever muscle relaxants are used with TIVA. iControl-RP and McSleepy are two automated CLADS. In iControl-RP, in addition to bispectral index (BIS), peripheral oxygen

saturation, heart rate, respiratory rate, and blood pressure are monitored and drug delivery is altered automatically based on these parameters. In McSleepy, all three components of general anaesthesia, like hypnosis, analgesia, and neuromuscular blockade, are monitored using BIS, Analgoscore, and train of four testing, respectively. Studies have shown better control of hypnosis and faster extubation with McSleepy system compared to manually administered anaesthesia **(17)**

- **Specialised infusion sets**

Specialised extension sets should be used during TIVA for better clinical effectiveness and patient safety. These sets should have a Luer-lock connector at each end, an anti-syphon valve on the drug delivery line, and an anti-reflux valve in the fluid administration line. In order to reduce dead space, one should also make sure that drug and fluid lines are placed as close to the patient as possible **(17)**

- **Mobile apps**

iTIVA and TIVAManager are computer programs created for monitoring plasma concentrations of anaesthetic drugs and guide the administration of TIVA. iTIVA is a pharmacokinetic/pharmacodynamic simulation programme based on mathematical models and calculates a dose required to achieve the target plasma, or effect-site concentration. As infusion schemes are obtained from published models, there are chances of wide variation in the plasma concentrations and clinical effects achieved. Currently, its use is limited to educational purposes to demonstrate pharmacokinetic principles. TIVA Manager has got added advantages like monitoring of concentrations of anaesthetics and planning of anaesthesia with TCI, availability of a wide range of pharmacokinetic/pharmacodynamic models, better optimisation of anaesthesia course by assessing the effect of administered drug, and availability of data for scientific investigations and education **(18)**

Limitations of Total Intravenous Anaesthesia

In spite of its many advantages, TIVA has many limitations. The anaesthesiologist must be aware of the potential drawbacks of TIVA. The most favoured TIVA drugs such as propofol and remifentanil are not devoid of adverse effects. One is likely to face problems such as the propofol infusion syndrome and hyperalgesia. TIVA in morbidly obese patients must be practised with extra precautions for a safe recovery from the accumulation of drugs **(19)**. Also, Difficult cannulation can hinder the administration of TIVA, especially in children, the obese, and the elderly. Pain on injection interferes with the use of certain agents in total intravenous sedation techniques. Bacterial contamination is known to occur with lipid-based emulsions like propofol, especially in prolonged procedures. Strict asepsis needs to be followed and change of the administration sets is recommended in prolonged infusions **(13)**.

Frequent misconnections leading to inefficient drug delivery have been reported in literature, leading to awareness during the procedures. To avoid this, all infusion lines should be visible and continuously monitored and checked every 15 minutes. TCI and depth of anaesthesia equipment are expensive and are not available in many centres. Though these equipment are a one-time investment to reap much greater benefits, the cost of drugs or disposable monitoring electrodes is not enticing. The favourable effect of TIVA in the environment is offset by the wastes generated, such as plastics, which cause additional greenhouse effects. Awareness during anaesthesia is an appalling complication that makes anaesthesiologists reluctant to use TIVA when adequate monitoring is not available. As there is no ability to monitor drug concentration in real time, uncertainty often exists when a combination of drugs and muscle relaxants are being administered. When it comes to managing haemodynamic instability and patients with opioid and benzodiazepine tolerance using TIVA, the choices are limited. Nonetheless, the chances of neurotoxicity with the prolonged administration of these agents are yet to be evaluated **(20)**.

The most common contributory factor for awareness under TIVA is inadequate education and training. Training in TIVA with a holistic approach should be a part of core anaesthesia training to ensure competency and safety in TIVA use. The Association of Anaesthetists and the Society for Intravenous Anaesthesia have recommended joint guidelines for the use of TIVA drugs, concentrations, infusion pumps, specific clinical scenarios, precautions, monitoring, and training for clinical practice. Similarly, there should be national or international guidelines for the safe, best, and easy practice of TIVA. The relevant anaesthetic organisations

should establish a set of standards and recommendations for the best practice of the use of TIVA, and the scope of TIVA can thus escalate in leaps and bounds. Research studies on TCI by Indian anaesthesiologists are still sparse and they need to gather more momentum so that more local data are generated and our own pharmacokinetic models can be generated based on our population genomics **(17)**

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