Total Intravenous Anaesthesia for War Surgery

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Abstract

Total Intravenous Anaesthesia (TIVA) and Target-Controlled Infusion (TCI) of anaesthesia are techniques that have benefited from recent advances in microprocessor technology and drug design. Though dependant on technology, they offer significant clinical benefits and logistic advantages. Manipulation of complex data derived from population pharmacokinetics has enabled greater understanding of drug handling models, thus enabling individual patient titration of anaesthesia. This has also informed manual techniques of intravenous anaesthesia. These approaches constitute a useful and logical alternative in the field, both in austere circumstances as well as the more established deployed setting. The pharmacodynamics and pharmacokinetics of potent intravenous anaesthesia agents in the complex combat trauma patient require continued examination.

Introduction

Total Intravenous Anaesthesia (TIVA) describes the technique of inducing and maintaining anaesthesia purely by intravenous means. The use of Volatile Gas Anaesthesia (VGA) is consequently avoided. Agents are delivered either by infusion or bolus to achieve the desired balance of hypnosis, analgesia and muscle relaxation.

TIVA for war surgery can be traced back to the use of barbiturates during the Spanish Civil War (1936-9). Despite being associated with an increased mortality rate in casualties of the attack at Pearl Harbour [1] (a proposition that has since been challenged [2]), British military anaesthetists successfully employed continuous thiopentone anaesthesia during World War II [3]. The use of ketamine during the Falklands conflict informed the development of TIVA regimes [4] and in the first Gulf War, further examples of TIVA were described [5, 6]. Advances in pharmacology and technology continue to inform and help refine its use in current conflicts. Table 1 outlines the areas in which TIVA is employed by the Defence Medical Services (DMS).

Pre-hospital care	During tactical transfer of intubated patients to the Field Hospital by the Medical Emergency Response Team (MERT)
Role 2/Role 3 surgical facilities	As a substitute for the more traditional VGA
Sedation	For intubated patients on the Intensive Care Unit (ICU) and during transfers to CT scan
During strategic transfer	For sedation of intubated patients to role 4 by RAF Critical Care Air Support Teams (CCAST)
Role 4 hospitals	For further surgical procedures (e.g. wound wash outs, second looks, reconstructive surgery)

Table 1. Operational areas in which TIVA is employed

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Comparison of TIVA against VGA for War Surgery

TIVA possesses certain desirable features for war surgery when compared with VGA and these are described below, followed by potential disadvantages.

Advantages of TIVA

Small Logistic Footprint

Deployed surgical teams work in austere conditions at the end of a long supply chain and must be prepared to move at short notice. Traditional anaesthetic machines are bulky, difficult to transport and require compressed oxygen and a power source to function. A method of waste gas disposal is also required. This is in contrast to a single programmable syringe driver, which can be carried in the pocket of a rucksack with space for additional batteries [7]. Even the battle-proven lightweight Tri-Service Apparatus (TSA) cannot boast this simplicity and is known for its 20 separate tube connections [8].

Recovery Characteristics

Provision of post-operative recovery facilities is highly limited in a deployed field hospital, both in terms of space and trained personnel. A technique that reduces the burden on anaesthetic and recovery staff is beneficial for the facility as a whole. Whilst speed of recovery from propofol-based TIVA may not be significantly different to that from VGA with the newer volatile agents desflurane and sevoflurane, a recent systematic review [9] found that nausea, vomiting, antiemetic use and headache were all lowest in the propofol group.

Modulation of the Stress Response

The stress response to surgery is characterised by increased sympathetic outflow, immunosuppression and a catabolic state. Attenuation of this response has become a treatment goal of peri-operative medicine. Compared with VGA, propofol-based TIVA has been shown to delay and reduce the rise in IL-6 [10] (a pro-inflammatory cytokine) and stress hormone levels [11] in response to surgery. The clinical benefits of this effect, and whether it exists in the military trauma population, remain to be characterised.

No potential for triggering Malignant Hyperthermia (MH)

MH is a rare but potentially fatal condition that is resource-heavy to treat. It may be triggered by halogenated volatile agents (or suxamethonium), but not by TIVA.

Continuity of anaesthesia

The continuity of agent delivery with TIVA has benefits both during and after the operative phase. At intubation there is no 'twilight period' as may occur in VGA between the offset of intravenous induction agents and the onset of volatile agents, reducing the risk of awareness [12]. Also, intraoperative manipulation of the airway will not disrupt the delivery of anaesthetic.

Severely injured patients who have undergone damage control surgery often remain intubated in the ICU and during CCAST transfer to Role 4. The sedation required to keep these patients stable can be delivered by the same TIVA infusion as was used for the initial surgery (albeit at a reduced dose). It makes pharmacological sense to avoid the haemodynamic instability that may arise when one form of sedation is changed for another [7].

Disadvantages of TIVA

Lack of familiarity

All DMS anaesthetists are expected to be proficient in the use of TIVA, but are likely to be more familiar with VGA. Opinion remains divided whether TIVA is an appropriate technique for use in the cold, shocked, coagulopathic military trauma patient. Some consider it to be relatively contraindicated during the immediate resuscitation phase and prefer the security of an end-tidal volatile agent concentration to titrate delivery of a haemodynamically stable anaesthetic.

Perceived risk of awareness

With VGA the end-tidal volatile agent concentration is measured, providing an assurance that anaesthetic is actually reaching the patient. By contrast, unrecognised disconnection and under-dosing are major considerations when using TIVA as there is no readily available clinical equivalent measure to the end-tidal volatile agent concentration. The closest would be the estimated blood (C_p) or effect (C_e) site concentration provided by a Target Controlled Infusion (TCI) pump.

It is advisable to use a dedicated intravenous line for the TIVA infusion that is visible throughout the operation.

Neuromuscular blockade increases the likelihood of awareness occurring since it prevents patient movement, a useful direct indication of nociception and indirectly one of inadequate anaesthesia. With TIVA, the use of muscle relaxants should be avoided or minimised where possible. Some advocate the use of a small dose of midazolam to reduce the risk of recall of awareness. Despite the above, the use of properly conducted TIVA/TCI is not associated with increased risk of awareness.

Need to service and power infusion pumps

Although TIVA represents a relatively small logistical requirement when compared with VGA, there is still the need to service, maintain and power infusion pumps. In the event of pump failure, TIVA regimes that require only a standard intravenous giving set have been proposed.

Dependant on intravenous access

By definition, intravenous access is required for TIVA. This is likely to be difficult in the shocked, unresuscitated military trauma patient where intraosseous access is normally the first technique used. Any drug may be given by this route (e.g. a bolus of ketamine), but an ongoing infusion would require intravenous access.

Drugs used for TIVA

Drugs available for use by DMS anaesthetists for TIVA consist of the anaesthetic agents propofol and ketamine. Thiopentone is available but is a poor choice for TIVA due to its tendency to accumulate within the body. Midazolam may be given by infusion to provide sedation in critical care patients but would rarely be used as a sole agent to maintain surgical anaesthesia. Some regimes include infusion of an opioid or muscle relaxant.

Propofol

Propofol is a phenol derivative that is thought to act by potentiating inhibitory gamma-aminobutyric acid (GABA) receptors. It is the most commonly used intravenous anaesthetic agent in Western medicine. Features that favour its use for TIVA in war surgery include:

- Familiarity
- Extensively characterised context-sensitive behaviour
- Low incidence of allergy
- Reduction in postoperative nausea and vomiting (consensus guidelines recommend its use in susceptible patients [13])

Drawbacks to its use include:

- Reduced cardiac output and systemic vascular resistance, which could be catastrophic in a shocked trauma patient. Dosage may need to be significantly reduced in such patients. A study of TIVA in a porcine model revealed that after haemorrhagic shock the blood propofol level increased by 375% in unresuscitated animals [14].
- Vulnerability to temperature damage. Propofol should be stored between 4°C and 22°C [15]. A study of a US helicopter drug box found that the temperature exceeded 25°C for 37% of the time during the summer [16]. One author's experience (SJ) during Operation TELIC was that a stock of propofol had almost solidified during its presumably unmonitored journey along the supply chain at the height of an Iraqi summer.
- Pain on injection

Ketamine

Ketamine is an intravenous anaesthetic agent derived from phencyclidine that acts via antagonism of N-methyl-D-aspartate (NMDA) receptors. It has many properties that favour its use within military and trauma anaesthesia, summarised by Grothwohl [17] as:

- Haemodynamic stability with no evidence of human *in vivo* myocardial depression)
- Reduced redistribution hypothermia [18]
- Maintenance of protective airway reflexes and respiratory function
- Bronchodilation
- Maintenance of the hypoxic pulmonary vasoconstriction reflex
- Analgesic effects (opioid synergy and reduced opioid tolerance)

Concerns over certain side effects have prevented its use becoming widespread within the UK [17]. They include:

- Increased ICP – which is now contested [19], ketamine may even be neuroprotective [20]
- Psychotropic effects - these may be reduced if benzodiazepines are used concurrently or as premedication. The S(+)-ketamine isomer may have reduced psychotropic effects whilst providing better analgesia than its R(-)-ketamine equivalent [21].

- Increased salivation and tracheobronchial secretions – these can be prevented or treated with an antisialogogue such as glycopyrrolate
- Prolonged recovery time

Recently the United States Tri-Services Anesthesia Research Group Initiative on TIVA (TARGIT) conducted a case-matched retrospective study of 214 cases of traumatic brain injury using data from their Joint Theatre Trauma Registry [22]. It compared those managed with ketamine-based TIVA against those who received VGA. They were unable to demonstrate a significant difference in neurological outcome.

Midazolam

Midazolam is a water-soluble imidazobenzodiazepine that acts at specific GABA-linked benzodiazepine receptors throughout the CNS. Its main actions are hypnosis, sedation, anxiolysis and anterograde amnesia. In bolus dose it has a short duration of action due to its high lipophilicity (at body pH) and metabolic clearance. With infusion it may accumulate and elimination half-life is significantly increased in the critically ill patient. There is also the potential for withdrawal phenomena after prolonged infusion, particularly in children.

In the context of TIVA for war surgery, midazolam is useful as an adjunct to a ketamine-based technique. Advantages include [23]:

- Reduced potential for recall of awareness
- Reduced psychotropic effects of ketamine
- Reduced postoperative nausea and vomiting
- Muscle relaxation
- Modest cardiorespiratory depression
- Reversibility with flumazenil

Opioids

Opioid infusions are often used as part of a TIVA technique. Studies examining the interaction of propofol and opioids have demonstrated a reduction in Cp50 [24, 25] (the plasma concentration of propofol required to prevent movement to a surgical stimulus in 50% of subjects – analogous to MAC). This propofol-sparing effect is useful as it allows a reduction in the amount of propofol administered and thus greater haemodynamic stability.

Remifentanil is now available to DMS anaesthetists and deserves special mention. It is a synthetic anilidopiperidine that acts as a pure mu-opioid receptor agonist. It is notable for its short context-sensitive half time of 3-5 minutes, regardless of the duration of infusion. Propofol TIVA with high-dose remifentanil provides a clean, rapid recovery that reduces the burden on recovery facilities. The obvious consequence of this property is that remifentanil will make no contribution to post-operative analgesia.

Future Areas of Development

Target Controlled Infusion (TCI) Pumps

TCI pumps employ microprocessor technology to administer an infusion regimen at rates determined by models derived from population pharmacokinetics. Modern pharmacokinetic models are based around a 'three-compartment model', where the central compartment represents blood and the other compartments represent tissues into which the drug may distribute. The momentary drug concentration displayed on the device is a trended estimate, not the actual tissue concentration. The three-compartment model is the basis for the step changes performed by the TCI device in response to alterations in target concentration by the anaesthetist (Figure. 1).

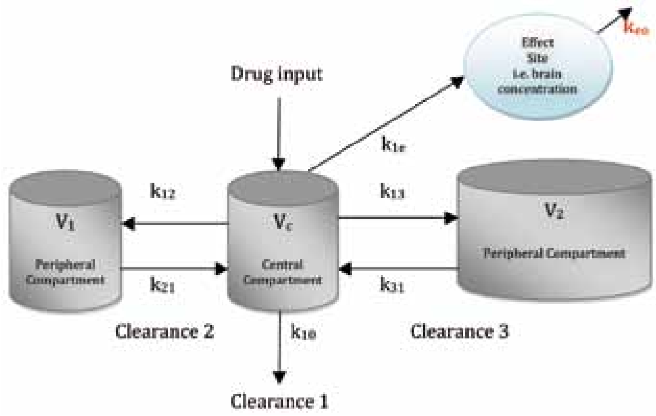

Figure 1: The traditional compartmental model of drug distribution with a continuous intravenous infusion. The effect site (represented by the blue compartment) is a recent addition that allows TCI systems to target brain concentration of drug. This compartment is considered volumeless for the purposes of mathematical modelling [26]

A detailed description of the practical aspects of using TCI techniques is beyond the scope of this article. However, two aspects of TCI that are central to safe practice are the pharmacokinetic models used and the site targeted. They are discussed below.

Pharmacokinetic Models

The two in widest use for propofol are the eponymously named Marsh and Schnider models. There are significant differences between them. The volume of the central compartment (V_c) used in the Marsh model is nearly four times greater than that of the Schnider model. The Schnider model allows for the slowed rate of distribution between V_c and V_1 (Figure 1). Though it has been suggested that the Marsh model correlates best for depth of anaesthesia [27], neither have been designed for use specifically in trauma patients. Failing to account for the altered pharmacokinetics of a patient with haemorrhagic shock could lead to dangerous overdosing and circulatory collapse. Reduced propofol and opioid requirements in haemorrhagic shock are thought to be partly due to decreases in central clearance and central and second compartment volumes of distribution [28]. Additionally, these models require patient parameters such as weight (and height in the case of the Schnider model), which can only be estimated in the immediate stages of treatment. This does not preclude the use of TCI in trauma patients, but constitutes an area of future research.

Targeting

Recognition of the need to titrate dosing strategies in order to influence the effect site (i.e. the brain) has driven the desire to target the effect site concentration. The newer generation of TCI pumps offer the ability to target effect site for both propofol and remifentanil. The effect site is considered volumeless for the purposes of mathematical modelling (Figure 1). For propofol, it needs to be appreciated that effect site targeting is based on certain critical suppositions arising from population pharamacokinetics, thus underlining the importance of "calibrating" the patient during induction. The benefits of utilising effect site targeting for remifentanil are yet to be determined and given the rapid equilibration achieved by remifentanil, may even be irrelevant.

The case for TCI pumps in the DMS

TCI pumps are not yet available to DMS anaesthetists, although the provision of this capability in the operational setting is likely to add value and is being actively pursued. The advent of 'open' TCI pumps has meant that generic propofol preparations can be used instead of expensive prefilled electronically-tagged syringes. Furthermore, the presence of a drugs library in these devices means that they are suitable for the safe infusion of other agents such as vasoactive drugs. The ability to deliver remifentanil and sufentanil as a TCI is an added feature of these newer "open" TCI pumps.

TCI pumps have been used successfully in the field by the Austrailian Army Medical Services in East Timor, who concluded that TCI is a useful substitute for VGA [29].

It is important that the user is aware of the ergonomics, capabilities and pharmacokinetic specifications of the chosen device, as there are important aspects of drug handling to be considered. An understanding of the chosen pharmacokinetic model is essential to the rational administration of the relevant drug. Three commonly available commercial "open" TCI systems are shown in Figure 2:

Figure 2: Commercially available open TCI systems

A current area of research is closed-loop TCI technology, whereby depth of anaesthesia monitoring is employed to provide direct feedback to the microprocessor and facilitate automatic infusion rate adjustment.

Depth of Anaesthesia Monitoring in the Field

Systems available to monitor depth of anaesthesia may be divided into cortical activity-based and evoked potential systems. The system that enjoys widest support in the literature is the Bispectral Index (BIS) system. An electrode strip placed across the forehead measures potentials arising from the activity of the patient's cerebral cortex. Data is integrated into an index between 0 (cortical silence) and 100 (fully awake). Values below 60 indicate clinical anaesthesia and those below 40 indicate a deep hypnotic state. This single variable is meant to correlate with behavioural assessments of sedation and hypnosis.

As a monitoring system, BIS possesses certain limitations. A study was published in 2003 in which the authors administered muscle relaxant to themselves without anaesthetic agent, reporting that the BIS score was actually seen to fall [30]. Also BIS is incompatible with ketamine-based TIVA. BIS score is actually seen to increase following bolus injection of ketamine [31].

Figure 3: The ASPECT™ BIS VISTA monitor in use together with a TIVA system on Operation TELIC 12

The case for a Depth of Anaesthesia Monitoring System in the DMS

Presently, clinical signs are the only guides that the DMS anaesthetist has to assess the adequacy of TIVA, though these are known to lack sufficient specificity and sensitivity to confirm depth of anaesthesia. The quoted incidence of awareness under anaesthesia ranges from 0.11% to 0.18% and haemodynamically compromised trauma patients are particularly at risk of under-dosage given the caution that is necessary when anaesthetising them. Likewise, over-dosage can lead to cardiovascular compromise and prolonged recovery. The situation is also complicated by the use of remifentanil, which whilst possessing no hypnotic properties of its own, appears to allow downwards titration of co-administered propofol. An American Society of Anaesthesiology (ASA) task force released a Practice Advisory in 2006 that recommended brain function monitoring should be considered in situations when there was an increased risk of intraoperative awareness, including trauma surgery [32].

The introduction of depth of anaesthesia monitoring may bring other benefits. A prospective observational study of over 1000 high-risk patients undergoing major non-cardiac surgery identified three independent variables as significant predictors of mortality [33]. These were patient co-morbidity, intra-operative systolic hypotension and cumulative deep hypnotic time (BIS < 45). BIS scores in this range generated a 24.4% relative risk of death per hour.

Technical Dependency	Agents	Indication	Method	Notes
'Low Tech' TIVA Regimes (without electronic infusion pumps)	Ketamine	Prehospital care, austere environments	0.5-2mg/kg iv for induction (use less than 1mg/kg if shocked). Maintain with 0.5mg/kg boluses or 20-100mcg/kg/min. 2mg midazolam reduces emergence delirium. 200mcg glycopyrrolate reduces salivation.	Full effect of bolus persists for about 10 minutes. In most cases airway reflexes and self-ventilation should be preserved.
	Propofol, Fentanyl and Ketamine [17]	Maintenance of general anaesthesia with TIVA when electronic infusion pumps are unavailable	40ml of 1% propofol, 5ml of 50mcg/ml fentanyl and 5ml of 50mcg/ml ketamine is mixed with 50ml of NaCl 0.9% (solution will contain 4mg/ml propofol, 2.5mcg/ml fentanyl and 2.5mcg/ml ketamine). Initially one drop every 3 seconds through a standard 20 drop/ml giving set and titrate to effect.	Relatively high concentration of ketamine therefore good analgesic properties and slow return to full arousal after discontinuing. Omit ketamine for more rapid emergence.
'Medium Tech' TIVA Regimes (electronic infusion pump required)	Ketamine and Midazolam [35] (+/- Vecuronium) [4]	Cardiac-stable regime in the haemodynamically compromised casualty. Allows invasive ventilation.	Induce anaesthesia with 1mg/kg ketamine plus 0.07mg/kg midazolam. Maintain by infusion of 200mg ketamine plus 5mg midazolam made up to 50ml and run at: (patient's body weight in kg/2)ml/hr 12mg vecuronium may be added for muscle relaxation.	The mixture has a 72 hour shelf life.
	Propofol and Alfentanil [5]	Invasive ventilation of casualties without haemodynamic compromise	50ml of 1% propofol and 2.5mg (5ml) alfentanil. Infuse mixture at an initial rate of 1ml/kg/hr following a standard induction. Reduce rate by up to half according to clinical signs.	Facilitates rapid emergence compared with isoflurane-based VGA [36]. Low incidence of nausea.
	'Classical' Manual Propofol Infusion [37]	Anaesthesia for casualties without haemodynamic compromise.	Initial bolus of 1mg/kg for induction then 10mg/kg/hour for 10 minutes, 8mg/kg/hour for 10 minutes followed by 6mg/kg/hour for subsequent maintenance of anaesthesia.	Low incidence of nausea. It has been estimated that this schema delivers a steady state concentration of around 3µg/ml.
'High Tech' TIVA Regime (utilising TCI technology)	Propofol and Remifentanil	Ventilated anaesthesia preferably without the use of neuromuscular blockade.	50ml 1% propofol infusion and a 40ml solution containing 2mg remifentanil. If TCI pump available for each drug: Initial blood propofol target 4 to 6µg/ml Initial remifentanil target 8 to 10ng/ml. If TCI is not available for remifentanil: Infuse remifentanil at 0.5µg/kg/min for 3 to 5 minutes followed by 0.25µg/kg/min. Maintenance rates range from 0.12 to 0.5µg/kg/min. Commence propofol first as a rapid rise in effect site concentration of remifentanil can induce apnoea before loss of consciousness.	The initial Cp or Ce target for propofol is chosen to be just above the anticipated concentration required for loss of consciousness in that patient. The concept of "patient calibration" is central to the success of this technique. Caution is required with these targets especially where there is cardiovascular instability. Estimated Ce should be noted at points during induction such as loss of response to command, instrumentation of the airway and incision. This will identify the Ce and Cp below which it would be inadvisable to drop and also helps identify the likely emergence point.

Table 2. Suggested regimes for TIVA in the field

A field trial of the ASPECT™ BIS VISTA monitor was conducted by one of the authors (SJ) on OP TELIC 12 in 2008. A photograph of this monitor in use together with a TIVA system is shown in Figure 3. Apart from one episode of diathermy-related interference the system performed well across a spectrum of anaesthetic procedures.

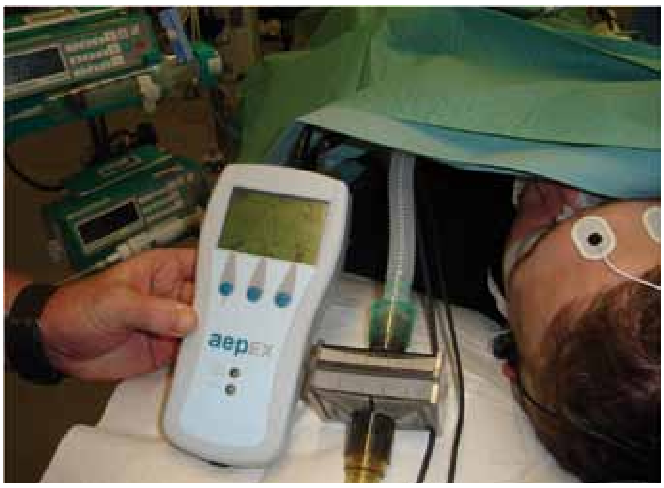

Figure 4: Depth of Anaesthesia monitoring employing auditory-evoked potentials during Operation TELIC 13

Direct injection of volatile agents into the bloodstream

This intriguing concept is still at the animal testing stage. Experiments using intravenous emulsified isoflurane have characterised potential advantages of this approach. Its use requires no specific ventilatory circuits or reliance on pulmonary function. There is evidence that onset and offset is faster than propofol-based TIVA whilst being very haemodynamically stable. A further benefit is the preconditioning effect that isoflurane elicits against ischaemia-reperfusion injury [34].

Suggested regimes for TIVA in the field

The method of TIVA used will be dictated by anaesthetist preference, clinical presentation and the availability of drugs and equipment. The regimes outlined in Table 2 are all 'battle-proven' techniques for use in adults that have been used by military anaesthetists. They also include approaches to TIVA for situations when electronic infusion pumps are unavailable.

Conclusion

There are some clear advantages of TIVA over VGA to the deployed military anaesthetist. The drugs and technique used can be tailored to both the patient's physiological status and the wider logistical situation in which the surgical team is working. Future developments may further enhance the applicability of TIVA for war surgery.

The purpose of this article is not to suggest that TIVA should replace VGA within the DMS, but to promote it as a valid alternative. It would certainly be wrong to assume that "…*anyone who could depress the plunger of a syringe in response to movement in a patient could give an anaesthetic*" [2]. There is great potential for harm with poorly administered TIVA, and advances in military pre-hospital care have meant that increasingly sick patients are now surviving to reach Role 2/3 facilities. When confronted with such patients, the best anaesthetic to give is probably the one with which the anaesthetist is most familiar, be that either VGA or TIVA.

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