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Empirical aspect of usage of total intravenous anesthesia

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Abstract
Target-controlled infusion (TCI) of propofol and remifentanil is "ideal" total intravenous anaesthesia because it effectively blunts the body's reaction to pain (TIVA). Since all propofol TCI models have been shown to be reliable in clinical practise, there is currently no proof to recommend using one over the other. For both the induction and maintenance stages of TIVA, it is crucial to titrate the effect-site dosage to patient response. Since TIVA produces a profound level of anaesthesia, a treated EEG device is typically recommended to avoid overhypnosis. TIVA raises consciousness when a drug is not given due to a technological glitch, so being on the lookout for this kind of mistake is crucial.

Keywords: Anaesthesia, infusion, PRIS, hyperalgesia

Introduction
An increase in the use of total intravenous anaesthesia (TIVA) has been aided by the development of sophisticated pharmacokinetic formulas for target-controlled infusion (TCI). Clinicians may opt to use a volatile agent instead of implementing TIVA due to its technical complexity and labor-intensive technique.

Pharmacological agents used for TIVA
Both opioid-free methods and those utilising i.v. hypnotics are discussed. For the purposes of this study, 'ideal' TIVA is defined as a combination of TCI infusions of propofol and remifentanil, both of which have been shown to be very effective at obtunding reactivity to noxious stimuli1. There is a happy medium between sufficient anaesthetic depth and speedy recovery with this medication cocktail. Manually regulated infusions or sporadic boluses of agents may not be sufficient.

Types of surgery
Listing 1 details the various uses for TIVA. TIVA can be used in nearly every surgical setting, but it shines in situations where a calm conscious withdrawal devoid of laryngospasm is a necessity. The Transient Intravenous Awakening and Amnesia (TIVA) approach has many benefits over the traditional volatile anaesthesia method, including a more favourable recovery profile and a decreased incidence of nausea and vomiting after surgery. Despite some safety concerns, TIVA is routinely used in situations where a rapid intubation procedure is needed.

Table 1: specific indicators for TIVA

Malignant hyperthermia risk
Long QT syndrome (QTc ≥ 500 ms)
History of severe PONV
'Tubeless' ENT and thoracic surgery
Patients with anticipated difficult intubation/extubation
Neurosurgery—to limit intracranial volume
Surgery requiring neurophysiological monitoring
Myasthenia gravis/neuromuscular disorders, and situations where NMBs are of disadvantage
Anaesthesia in non-theatre environments
Transfer of an anaesthetised patient between environments
Daycase surgery
Trainee teaching
Patient choice

Choice of propofol TCI model

The primary factors in selecting a propofol TCI model are the patient's age (if they are younger than 16 years old) and the accessible programming in commercial infusion devices. None of the models have been shown to be less reliable than the others in clinical settings, and there is currently no proof to recommend using one over another. Both the accuracy and consistency of the projected plasma and impact concentrations suffer from the same problems across all models. Most anesthesiologists have practise with Marsh plasma-targeted injections for sedation, so they take comfort in the fact that TIVA follows a similar model, only with a higher drug mass administered for a given numerical goal (Table 2). As expertise and self-assurance grow, practitioners shift towards models that account for the Schnider as well as modified Marsh effect.

Table 2: Comparison of the bolus dose of propofol and subsequent infusion rate administered to a male patient, 177 cm and 85 kg by three TCI models when the target is set at 3.5 pg m1-1. Data derived from Tivatrainer 9 software (www.eurosiva.eu)

Patient age (yr)	Effect-targeted Schnider		Effect-targeted modified Marsh		Plasma-targeted Marsh	
	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h-')
40	63	830	100	1040	71	1100
80	53	670	100	1040	71	1110

Starting the infusions

The common question from a TIVA newbie is "are propofol and remifentanil infusions begun simultaneously?" The response may vary based on who you ask; seasoned TIVA practitioners all have their own preferred induction recipe.

When both agents are to be administered via effect-site targeting, the response is unambiguous; however, when a propofol paradigm is utilized alongside remifentanil in plasma-targeted mode, the picture is more nuanced. When both drugs are administered concurrently, the concentration of propofol at the site of action rises much more quickly than that of remifentanil, making early synergy between them difficult to achieve. You could also try initiating remifentanil first to enable for phase transition at the impact before beginning propofol. Since anaesthesia can be obtained at reduced propofol effect-site concentrations, this expedites subsequent induction. Prevention of apnea necessitates both effective pre-oxygenation and frequent cues to the patient to take deep breaths.

Remifentanil recombines at the adverse affect much before propofol when injections of the both agents are begun simultaneously with plasma targeting. However, except if the propofol objective is substantially "over-pressured," the patient may be apneic but still conscious. This latter method has the same potential cardiovascular effects as a big manual bolus. As was discussed previously, there are advantages and disadvantages to beginning propofol after allowing remifentanil to reach the effect site.

Selecting TCI targets

It is possible to obtain the desired clinical effect by selecting either a high propofol/low remifentanil effect-site concentration or the reverse. 1 A faster recovery time can be achieved with a moderate propofol/high remifentanil combo, but this is often accompanied by apnea and the need for mechanical ventilation. Instead of letting a patient ingest a volatile agent on their own, many doctors use this combo for quick cases. Given that remifentanil has minimal hypnotic effects, it is suggested that a minimal impact propofol dosage of 2 g ml1 (for patients >50 yr of life) or 3 g ml1 (for patients 50 yr of age) be maintained for the majority of the patients. Although effect-site concentrations for propofol and remifentanil TCI can be proposed (Table 3), they cannot be guaranteed to be universally effective due to the wide variation in clinical response between individuals (see example in Fig. 1).

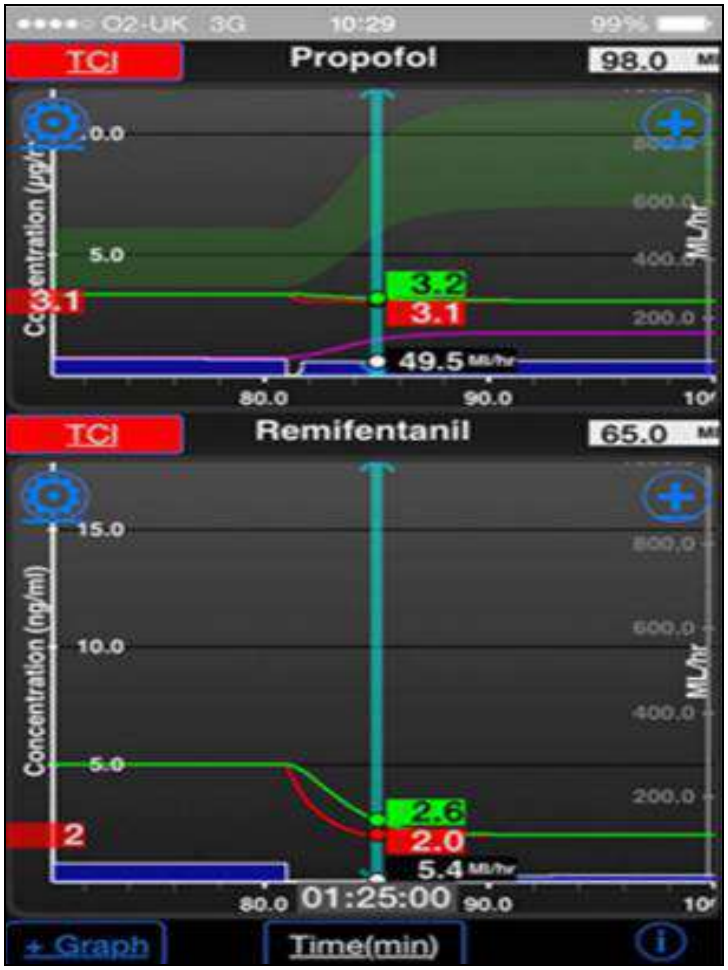

Fig 1: Screenshot from an Apple iPhone showing the perioperative use of Tivatrainer 10 software (www.eurosiva.eu). In this example, the drugs were administered using plasma-targeted models.

Table 3: Suggested minimum effect-site concentrations for TIVA in adult patients. These targets must be increased or decreased depending on individual patient response and/or processed EEG data

Suggested effect-site concentrations for TIVA				
Age (Yr)	Spontaneous breathing		IPPV	
	Propofol (µg ml-1)	Remifentanil (ng ml-1)	Propofol (µg ml-1)	Remifentanil (ng ml-1)
<50	4-6	1-3	3-4	5-8
>50	2-4-	1-2	2-3	3-6

Monitoring TIVA

Currently, there is no feasible method for monitoring propofol plasma amounts in real time. Noting increases in effect-site concentrations that demonstrate:

- Loss of response to trying to shake and shouting;
- Loss of haemodynamic reaction or limb motion with vigorous jaw thrusting3;
- Utter lack of tachycardia and even bradycardia to laryngoscopy and intubation can be used for clinical measurement of the individual patient prior to 'knife-to-skin.

The lowest and highest goals can be informed by three reference points provided by this approach. If muscle paralysis is necessary, it should be administered only after the patient no longer reacts to a jarring of the mandible. Since over-hypnosis is more prevalent than under-hypnosis during surgery, it is crucial to titrate effectsite dosage to patient response. Drug amounts at the site of action can be predicted in real time with the help of Tivatrainer pharmacokinetic software (www.eurosiva.eu). Using propofol and remifentanil TCIs together, this software graphically depicts the 50% and 95% probabilities of non-response to a noxious event (equivalent to 1 and 2 MAC for volatiles) (Fig. 1). Processed EEG data will identify excessive hypnosis but is not a reliable predictor of reaction to noxious stimulus, complementing clinical opinion and software predictions. 4

ASA status and advanced age

When it comes to inducing a profound state of anaesthesia, TIVA is second to none. This method still gives the best chance of recuperation profile, but it must be used with caution when patients are compromised by advanced years or poor ASA status. When comparing the Schnider effect model to the Marsh kinetics, the latter results in a lower dose of propofol being administered (Table 2) for any given numeric goal (despite the prediction of higher peak plasma concentration). Some medical professionals believe this is beneficial in the elderly because it reduces the risk of hemodynamic adverse effects. Age is accounted for in the Schnider model as a moderating element for both the bolus

dose and the infusion rate. However, as shown in Table 2, this makes only a marginal difference in the total dose of drug given, and thus cannot be depended upon to prevent an overly intense cardiovascular response. When using the Minto model for impact targeting, the bolus dosage is approximately three to four times greater than that when targeting the plasma. A greater plasma concentration can cause rigidity in the chest wall or severe bradycardia through processes other than the vagus nerve. Therefore, addressing the Minto effect is most appropriate for healthy younger patients. Regardless of the specific models employed, it is recommended that the ultimate impact dosage of both drugs be increased gradually in frail individuals. Before each goal raise, the doctor must check the patient's alertness and heart rate.

Setting up and using TIVA equipment

Most instances of anaesthetic awareness when using TIVA have been attributed to technical failure, according to the RCoA's Safe Anaesthesia Liaison Committee and the NAP5 investigators. Tables four and five suggest ways to further apply what has been learned from these works. TCI infusion devices need to be checked as carefully as the anesthesia machine.

Table 4: checklist for setting up TCI systems

1. Use only dedicated pharmacokinetic TCI pumps
2. Ensure that you are trained in use of the chosen pump and pharmacokinetic model
3. Ensure the pumps have been serviced in the past 12 months
4. Ensure the pumps are plugged into the mains
5. Ensure the batteries are charged
6. Ensure that the drug dilutions are correct and are entered correctly into the pump
7. Ensure that the correct syringe type and size data are entered and that the syringes are mounted correctly
8. Ensure that the pump is programmed for the drug actually attached to it
9. Ensure that the low and high infusion pressure alarms are set (to warn of disconnection and a 'tissued' cannula, respectively)
10. Ensure that the correct patient data are entered
11. Consider if the targets set are appropriate to the patient's age and ASA status
12. What is plan B if the pump(s) fail?

Table 5: Recommendations for precenting technical problems with TIVA

1. Complete the TCI system checklist
2. Affix the i.v. cannula firmly to the patient's skin
3. Keep the site of TIVA infusion visible so that disconnection, leakage, or a 'tissued' cannula are readily detected
4. Use only a dedicated two- or three-way TIVA set which incorporates • anti-siphon valves on the drug administration lines • non-return valve on any i.v. fluid line • minimal dead space distal to the point of agent and/or i.v. fluid mixing
5. Use only Luer lock syringes for administering drugs
6. Do not label the remifentanil syringe until the drug has been added to the diluent
7. Always check the infusion site if a pump alarms (except 'syringe empty', 'infusion paused', or 'mains failure')
8. Flush TIVA drugs from the dead space of a three-way administration set before connection to the patient cannula, and out of the cannula at the end of the case

Failure of pump programming

Upon total loss of both main supply and battery power, most commercially available TCI devices 'forget' their settings. Clinician has three choices, all of which are problematic;

To fall back on a method that relies on volatile molecules, which increases the risk of an exaggerated haemodynamic reaction due to synergistic effects among propofol, remifentanil, and volatile particles at the effect-site.

When electricity returns, use the millilitres per hour values shown on the device's display to restart the compressor in manual mode. Otherwise, the effect-site concentration won't be high enough, so the clinician will need to compute another dose prior to actually increasing the infusion rate if a dramatic rise in target is needed.
Pump should be restarted in TCI mode. Unless the selected target is valerate upwards incrementally, the device will be unaware of the drug already existing at the effect-site, leading to an exaggerated haemodynamic response.

Terminating the infusions
As the operation draws to a close, it makes sense to reduce TCI targets, but the closure of some wounds causes intense noxious stimulation if locoregional techniques are not used. Reductions in goals should not be made unnecessarily in order to hasten the healing process (Fig. 1). Again when the final sutures have been placed, it is generally safer to cease the infusions. If wanted, the remifentanil drip can be kept going at a target of 1-2 ng ml1 to make extubation go smoothly. Patients receiving large doses of morphine or using the Marsh model on obese subjects may experience delayed recovery after TIVA. Patients may need to be actively encouraged to open their eyelids and take spontaneous breaths after being sedated with TIVA drugs at subanaesthetic concentrations and remaining happy to receive assisted ventilation. After extubation, apnea can occur if remifentanil hasn't left the brain entirely.

Potential problems with TIVA
Awareness
Even though there is scant proof to back up the claim that lack of awareness is the main reason doctors don't use TIVA, this is the most common explanation given by clinicians. Analysis of the results of several major studies The variability in treatment regimens and methods categorised as "TIVA" complicates the situation at 5 and 6. (Errando and Zhang, personal communications). Similarly, inhalation anaesthetic awareness experiments should logically exclude the use of a "oxygen/nitrous oxide/no volatile" technique. Very few well-designed studies on consciousness during TIVA have failed to find an uptick in occurrence. Research on an isolated forearm method shows that patients given TIVA or volatile anaesthesia indicator solution to bispectral index have similar rates of responsiveness. 10 11 According to the NAP5 study, the majority of TIVA incidents can be traced back to technical mistakes and improper application of knowledge; if proper education and training had been provided, 75% of these incidents could have been avoided. On the other hand, NAP5 identified a halt in liquid anaesthetic administration as the primary cause of unintended consciousness. The 'gap' phenomenon associated with volatile agent application could have been avoided with the use of 'ideal' TIVA devoid of technical errors, thus preventing nearly all of these instances. NAP5 stressed the importance of using a packaged EEG device when providing TIVA, as suggested by NICE, for patients who need neuromuscular paralysis. The greatest advantage of employing these devices during TIVA, however, is likely to be that they keep patients from experiencing too much hypnosis. 12

Morbid obesity
Even though the current TCI models have not been officially validated for use in morbidly obese patients, the treatment of morbidly obese patients with TIVA is a challenging but common practise. Although this can typically be increased with the manufacturer's proprietary software, pump manufacturers place a cap of 150 kg on the amount of weight that can be fed into the Marsh model. On the other hand, a bolus dose that is based on the patient's actual body weight is very likely to be a substantial overdose and to bring about undesirable cardiovascular side effects during induction. Because these models use the "James equation" to determine lean body mass, the Schnider and Minto kinetics give rise to a different problem than the one described above (LBM). When the body mass index (BMI) of a person is greater than 42 for men and 35 for women, this equation produces a number for LBM that paradoxically decreases. Because the derived LBM is so essential to the pharmacokinetic calculations, manufacturers place restrictions on the input of anthropomorphic data that go above and beyond these sex-specific BMI values. When using the Schnider model, the reaction kinetics for renal excretion from the central compartment, known as K10, is adjusted for LBM. As a result, the injection rate that is applied is capped as actual body weight continues to rise. If the BMI was higher than the threshold number, the correction made to the intravenous infusion would not be sufficient, and the elevated rate of drug delivery could potentially generate heightened haemodynamic effects. In contrast, the Minto model predicts that the volume of the central compartment, the volume of the quickly equilibrating compartment, and the K10 rate constant will all increase proportionately with the LBM. When the patient's body mass index was greater than the critical number, the pump would gradually lower the bolus dose and the infusion rate, and an insufficient amount of analgesia would be delivered. There has been research conducted to determine the 'correct' body mass to use when administering TIVA, and at the moment, the Servin formula for determining an input mass for TCI infusions appears to be the most helpful.

Input mass = ¼ (ideal body weight) + 0.4 × (actual ideal)

Propofol, however, is extremely lipid-soluble, so the extra fat in morbidly obese people serves as a sink for the agent, allowing it to diffuse out of the plasma and into the fat cells. Theoretically, a patient's actual body weight is needed to calculate an infusion rate that keeps the intended plasma or effect-site content; under-prediction has been shown in some studies using "ideal mass" derivatives. 13 For individuals with real body weights of 5-160 kg, a morphometric propofol TCI model has recently been outlined, which may one day make TIVA safe and effective for the morbidly obese. The morbidly obese appear to be at a higher risk of accidental consciousness even before antimitotic drugs are used, so care must be taken when administering TIVA to this population at this time. Both NAP5 and NICE suggest using processed EEG monitoring in morbidly obese patients as part of continuous clinical assessment.

Analgesia and hyperalgesia
Several studies have stressed the importance of administering morphine between 0.15 and 0.3 mg kg1 and ending a remifentanil infusion at least 30-40 minutes before

morphine administration. A recent meta-analysis explored the issue of acute opioid tolerance following remifentanil and found that high intraoperative concentrations are linked to modest but statistically significant rises in acute pain following surgery. 14 TIVA is most effective when combined with non-opioid analgesics and locoregional techniques, as well as fentanyl "rescue" in the immediate postoperative phase.

Propofol-related infusion syndrome

Rhabdomyolysis, hypertriglyceridemia, and renal failure are all symptoms of propofol-related infusion syndrome (PRIS), which is characterised by severe metabolic acidosis and cardiac dysfunction. There have been no reported cases of PRIS in patients taking TIVA, as of yet. According to three case reports, doctors stopped using the TIVA method on an adult after discovering metabolic acidity. On the other hand, these individuals never developed any additional PRIS symptoms. Although PRIS is more common in children when they are subjected to propofol sedation in an intensive care setting,15 its use in paediatric therapy is deemed safe and perhaps an ideal technique.

Conclusion

If a patient needs general anaesthesia but is at danger of malignant hyperthermia, TIVA is the treatment of choice. A high risk of exposure is almost inevitable if the method's use is poorly taught and supervised. Most of this danger can be avoided if TCI uses propofol and remifentanil and follows some basic guidelines.

Conflict of Interest

Not available

Financial Support

Not available

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