

A retrospective case series of computer-controlled total intravenous anaesthesia in dogs presented for neurosurgery

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ABSTRACT

This article describes the anaesthetic management and use of total intravenous anaesthesia (TIVA) for neurosurgery in 4 dogs. Propofol in conjunction with morphine was used for the maintenance of anaesthesia. Anaesthesia was induced with either thiopentone or propofol. The program Stelpump (a target-controlled infusion program) was run on a laptop and connected to a syringe driver via an RS 232 cable. The program was found to be reliable and safe for the administration of TIVA in dogs. Invasive monitoring was required in order to monitor cardiovascular changes during surgery. Ventilation was controlled to maintain the end-tidal carbon dioxide below 40 mm Hg. The anaesthesia was characterised by haemodynamic stability. The haemodynamic stability was probably the result of the choice of TIVA and balanced anaesthesia. Intracranial pressure and oedema was controlled with dexamethasone, mannitol and ventilatory management either in combination or alone. Three dogs survived to hospital discharge and 1 dog was euthanased 2 weeks later due to tumour metastasis. The development and characterisation of the anaesthetic effects of TIVA needs to be elucidated in order to provide clinicians with rational guidelines for the appropriate use of TIVA in veterinary medicine.

Key words: balanced anaesthesia, computer target infusion, neurosurgery, propofol, TIVA, total intravenous anaesthesia.

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and the anaesthetic technique, was obtained from all owners as the technique was novel in the hospital. All dogs were clinically healthy as determined by serum chemistry, haematology and clinical examination except for neurological abnormalities associated with their individual conditions. The signalment of the 4 dogs is contained in Table 1. Dogs 2, 3 and 4 received dexamethasone (Kortico, Centaur Laboratories, Halfway House) (0.5–1.0 mg/kg divided into 3 doses over 24 hours) before surgery. Dogs 2 and 4 received phenobarbitone (Lethyl, Aspen PharmaCare, Johannesburg) to control seizures before surgery. Dog 4 was receiving cimetidine (Tagamet, Glaxo-Wellcome, Midrand) for gastric ulceration before surgery.

An intravenous catheter (Jelco, Johnson & Johnson Medical, Brussels) was placed in the cephalic vein for the administration of drugs. All dogs were premedicated with diazepam (Pax, PharmaCare Ltd, Port Elizabeth) (0.2 mg/kg i/v) and morphine (Micro Morphine, Micro HealthCare (Pty) Ltd, Bethlehem) (0.4 mg/kg s/c) 20 minutes before induction of anaesthesia. Additional doses of morphine (0.2 mg/kg) were administered every 2 hours thereafter until the end of surgery. Amoxicillin and clavulanic acid (Clamentin, Xixia Pharmaceuticals (Pty) Ltd, Halfway House) (20 mg/kg i/v) was administered immediately before induction of anaesthesia and then every 4 hours for the duration of anaesthesia. Anaesthesia was induced in 3 dogs with thiopentone (Intraval Sodium, Rhône-Poulenc, Halfway House) until conditions were optimal for intubation. In the remaining dog, anaesthesia was induced with propofol (Diprivan 1%, AstraZeneca Pharmaceuticals, Sandton), targeted by a computer to the minimum infusion rate (MIR) determined from the previous 3 dogs. After induction of anaesthesia, all dogs were intubated and allowed to breathe 100% oxygen from a circle breathing circuit with a fresh gas flow of 3 times metabolic oxygen demand ($3 \times 10 \times \text{BM}$ (BM = body mass)). A targeted continuous-rate infusion of propofol was immediately started following intubation.

INTRODUCTION

Much debate has occurred in the human medical literature concerning the optimal anaesthetic technique for patients undergoing neurosurgical procedures. Volatile anaesthetics alone are not considered optimal as they increase cerebral blood flow and increase intracranial pressure⁷. Volatile anaesthetic agents used in combination with opioids, sedatives and low doses of intravenous anaesthetic agents are acceptable for most neurosurgical procedures⁷. A technique of using total intravenous anaesthesia (TIVA) is suggested for such cases⁷. Intravenous anaesthetic agents offer the advantage of reducing cerebral oxygen consumption and cerebral blood flow but do not alter intracranial compliance⁷. Cerebral blood flow autoregulation, blood flow metabolism coupling and carbon dioxide responsive-

ness remain intact during TIVA^{7,16}. Ketamine is the only intravenous anaesthetic agent that may have detrimental effects on cerebral metabolism for neurosurgery⁷.

Propofol has been shown to be an acceptable anaesthetic agent for both neurosurgical procedures⁷ and total intravenous anaesthesia in dogs^{1,5,10,12,13,19,22,23,26,28,32,33}. The description of computer-targeted infusion of propofol has recently been described^{2,20}. In veterinary medicine, limited information is available on suitable anaesthetic techniques for oncological neurosurgery^{11,14}. The intention of this study was to evaluate retrospectively the stability and safety of the computer-targeted infusion system for neurosurgery.

MATERIALS AND METHODS

Four dogs undergoing neurosurgical procedures admitted to the Onderstepoort Veterinary Academic Hospital were identified for inclusion where total intravenous anaesthesia with propofol was to be used for the maintenance of anaesthesia. Informed consent, for the procedure

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Table 1: Signalment of 4 cases presented for neurosurgery.

| Number | Breed | Age | Sex | Mass (kg) | Condition |
|--------|---------------------|----------|--------|-----------|-----------------------------|
| 1 | Boerboel | 9 months | Male | 26 | Cervical dorsal laminectomy |
| 2 | Labrador | 6 years | Female | 20 | Cerebral meningioma |
| 3 | Boxer | 7 years | Male | 39 | Cerebral astrocytoma |
| 4 | German shepherd dog | 4 years | Male | 46 | Cerebellar melanoma |

Table 2: Pharmacokinetic parameters constructed from a computer model by Beths *et al.*²

| Parameter | Value |
|---------------------------|--------|
| V _c (l/kg) | 0.780 |
| Cl (ml/kg/min) | 54.6 |
| K ₁₀ (minutes) | 0.07 |
| K ₁₂ (minutes) | 0.0365 |
| K ₂₁ (minutes) | 0.0312 |
| K ₁₃ (minutes) | 0.0049 |
| K ₃₁ (minutes) | 0.0011 |

A pharmacokinetic infusion program, Stelpump^a, was programmed with the validated computer pharmacokinetics of propofol by Beths *et al.*² (Table 2). A Pentium III laptop computer with 128 MB of RAM (Latitude CPxJ, Dell Computer Corporation, Ireland) was used to run the pharmacokinetic infusion program. The computer was connected to an infusion pump (Graseby 3400, Graseby International) through an RS232 cable wired according to the instruction given with the program. Bolus doses of propofol were administered at a rate of 1200 ml/hr with the remaining infusion rates determined by the computer program. The propofol concentration was 10 mg/ml and the delta T for the computer was 10 seconds. The time, predicated plasma propofol concentration and pump rate was recorded every 0.17 seconds for the duration of the study in a log file generated by the pharmacokinetic infusion program. The initial target concentration of propofol was 5.0 µg/ml.

After the induction of anaesthesia, a triple lumen central line (Arrow-Howes Multi-lumen Central Venous Catheterisation Set, Arrow International, Reading) was placed in the external jugular vein. Propofol was infused through the proximal port, normal saline (0.9 % Sodium chloride, Frasenius Kabi, Port Elizabeth) the middle port and central venous pressure was measured through the distal port. Normal saline was administered at a rate of 80 ml/kg/day (Inca Pump, Frasenius Kabi, Schweinfurt). Fluid rates were adjusted according to blood loss and central venous pressure. Central venous pressure was kept between 4 and

10 cm H₂O. The dorsal pedal artery was cannulated with a 20 G intravenous catheter (Jelco, Johnson & Johnson Medical, Brussels). Blood pressure was measured through the arterial catheter. Pressure transducers (DTX, Becton Dickinson Critical Care Systems, Singapore) were placed at the level of the heart. The flush solution (1 l normal saline with heparin (Heparin Sodium, Frasenius Kabi) 1 iu/ml) was pressurised to 300 mm Hg. Pulse oximetry, blood pressure, central venous pressure, oesophageal temperature and electrocardiogram were monitored (Life Scope P, Nihon Kohden, Tokyo). A capnograph (Capnomac Ultima, Datex-Ohmeda, Helsinki) sampling tube was placed onto the end of the endotracheal tube to monitor end-tidal carbon dioxide concentrations. Ventilation was controlled with positive pressure ventilation (Penlon AV800, Penlon, Oxon) to ensure that end-tidal carbon dioxide concentration remained below 40 mm Hg. Body temperature was kept at 37.0 °C. A warm-water circulating blanket (Nor-O-Temp, Cincinnati Sub Zero, Cincinnati) was used as required. Cooling of the body temperature was initially allowed. Respiratory rate and tidal volume were adjusted accordingly with the peak inspiratory pressures limited to 20 cm H₂O. A urinary catheter was placed and the bladder drained. Urine output and blood loss was then measured every 20 minutes. Lost blood was replaced with whole blood from donor dogs. All physiological parameters were monitored continuously and recorded every 10 minutes.

Anaesthetic depth was estimated based on the patient's response to surgical stimulus, changes in physiological variables (heart rate and blood pressure), muscular tone (jaw and limbs), neurological reflexes (palpebral and limb with-

drawal reflex) and voluntary respiratory efforts. Based on these signs, anaesthesia was assessed to be either adequate or inadequate. If anaesthesia was inadequate, the target-controlled infusion was increased by 0.5 µg/ml. If the anaesthetic depth remained adequate for more than 30 minutes or anaesthetic depth was judged to be too deep, the infusion rate was decreased by 0.5 µg/ml. The start and end times of anaesthesia and surgery were noted. All other drugs administered during anaesthesia were recorded.

Descriptive statistics were performed on the data (SigmaStat 2.0, Jandel Corporation, San Rafael). Physiological variables were analysed for 230 minutes, as 3 points of data were available for each ten-minute time interval. No further statistical analysis was done due to the limited number of cases and the absence of comparative data.

RESULTS

In the 3 dogs anaesthetised with thio-pentone, 9.1 ± 2.1 mg/kg was used. Anaesthesia was maintained in an adequate plane throughout. A target concentration of 5.0 µg/ml of propofol was used to anaesthetise the 4th dog, based on the mean target infusion rate used in the previous 3 dogs. The mean target infusion rate used in this study was 4.68 ± 1.00 µg/ml. Anaesthetic and surgery times are given in Table 3.

Physiological variables monitored are presented in Table 4. Blood pressure was well maintained with a mean blood pressure of 97.24 ± 9.87 mm Hg in all 4 dogs (Fig. 1). Dog 4 had a Cushing's reflex with a peak systolic blood pressure of 227 mm Hg and a decrease in heart rate to 65. Dog 4 was hyperventilated to control brain oedema to an EtCO₂ of 30 mm Hg for 45 minutes before returning to just

Table 3: Anaesthetic and surgery times for the 4 cases undergoing neurosurgery.

| Patient | Anaesthetic time (minutes) | Procedure time (minutes) |
|---------|----------------------------|--------------------------|
| 1 | 305 | 210 |
| 2 | 305 | 225 |
| 3 | 225 | 140 |
| 4 | 350 | 220 |
| Mean | 296.25 | 198.75 |
| SD | 52.021 | 39.660 |

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Table 4: Physiological variables monitored. All data are given as a mean.

| Patient | Heart rate (bpm) | Blood pressure | | | SpO ₂ (%) | Respiration (bpm) | EtCO ₂ (mm Hg) | TV ml/kg | CVP (cm H ₂ O) | Urine (ml/kg/hr) | Fluids (ml/kg/hr) | Blood loss (ml/kg/hr) | Temperature (°C) | Propofol µg/ml |
|---------|---------------------|---------------------|----------------------|-----------------|-------------------------|----------------------|------------------------------|-------------|------------------------------|---------------------|----------------------|--------------------------|---------------------|-------------------|
| | | Systolic (mm Hg) | Diastolic (mm Hg) | Mean (mm Hg) | | | | | | | | | | |
| 1 | 58.46 | 152.96 | 70.29 | 85.50 | 98.54 | 11.00 | 37.96 | 14.52 | 7.75 | 2.10 | 3.02 | 23.08 | 35.78 | 4.04 |
| 2 | 50.81 | 172.26 | 74.74 | 93.07 | 100.00 | 14.26 | 40.89 | 15.83 | 4.70 | 6.56 | 3.06 | 37.00 | 37.93 | 5.67 |
| 3 | 63.41 | 186.35 | 88.76 | 107.53 | 98.67 | 12.47 | 39.35 | 8.01 | 5.29 | 25.90 | 2.05 | — | 36.36 | 3.43 |
| 4 | 107.21 | 185.47 | 81.58 | 102.84 | 96.96 | 28.00 | 38.79 | — | 8.42 | 3.82 | 2.57 | — | 38.41 | 5.05 |
| Mean | 69.97 | 174.26 | 78.84 | 97.24 | 98.54 | 16.43 | 39.25 | 12.79 | 6.54 | 9.60 | 2.68 | 15.02 | 37.12 | 4.56 |
| SD | 25.35 | 15.59 | 8.08 | 9.87 | 1.250 | 7.83 | 1.24 | 4.19 | 1.82 | 11.02 | 0.47 | 18.25 | 1.25 | 1.00 |

SpO₂ = pulse oximetry saturation, EtCO₂ = end tidal carbon dioxide, TV = tidal volume, CVP = central venous pressure, bpm = beats per minute or breaths per minutes.

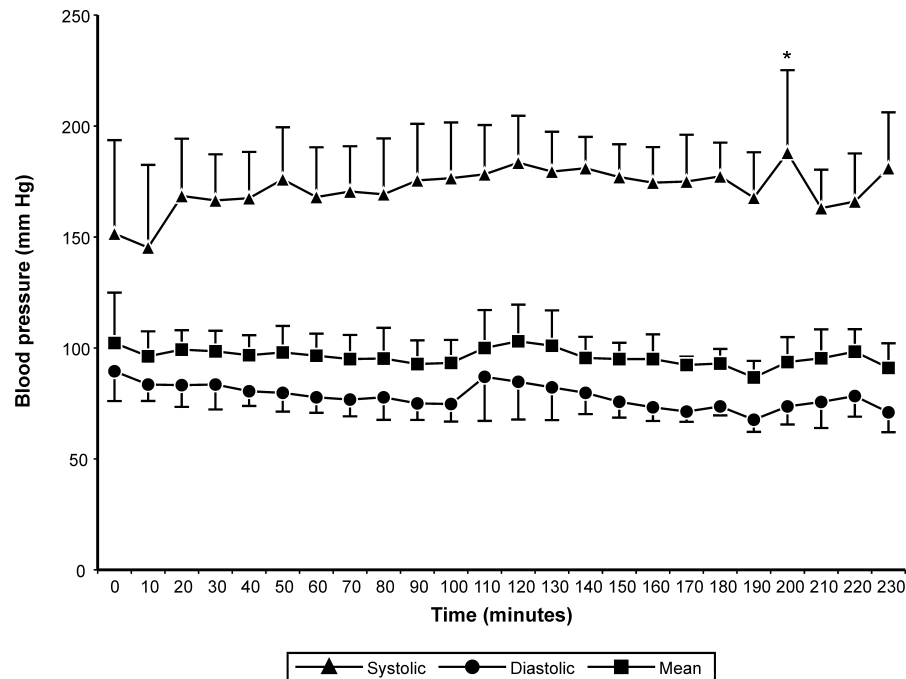


Fig. 1: Blood pressure (error bars indicate standard deviation). The asterisk indicates the point where Dog 4 underwent a Cushing's reflex.

below 40 mm Hg. Mannitol (Mannitol 0.5 g/l, Frasenius Kabi, Port Elizabeth) (0.5–1 g/kg) was administered in Dogs 2 and 3 to control brain oedema. The mannitol was associated with an increase in urine output. Dogs 1 and 2 required the administration of blood due to sinus bleeding. All dogs were doing well 48 hours after surgery. Dogs 1, 2 and 3 were discharged from hospital while Dog 4 was euthanased 2 weeks after surgery due to tumour metastasis.

Only one problem was encountered with the computer-controlled infusion system when the syringe stuck and as a result no propofol was administered. The program was found to be easy to use and refilling the syringe with propofol was simple to perform. After each syringe change, a bolus of propofol was administered to return predicted plasma concentration to target levels.

DISCUSSION

Although no conclusive decisions can be made from this small study about the use of TIVA for patients undergoing neurosurgery, a number of important differences between inhalational anaesthesia and TIVA are evident. These differences highlight some of the important clinical differences between the two methods to maintain anaesthesia and these differences may be relevant to other patient populations.

Inhalational anaesthetic agents are known to decrease cardiac output and blood pressure in a dose-dependent fashion^{4,19,30,31}. During neurosurgery, the maintenance of cerebral perfusion pressure

(mean arterial pressure less intra-cranial pressure) is critical for a successful outcome⁷. An adequate cerebral perfusion pressure of at least 60 mm Hg is required⁷. From the collected data, it is evident that blood pressure was well maintained and at times tended towards hypertension. The blood pressure data is slightly higher than that reported as normal for dogs⁸ but is similar to data obtained in healthy dogs^{17,18}. Stable blood pressure following the continuous administration of propofol has been reported^{1,9,19,26}. This opinion is not held by all as a decrease in blood pressure and cardiac contractility has been shown^{3,29}. When inhalational anaesthesia has been compared to propofol in dogs for the maintenance of anaesthesia, propofol was shown to cause a significantly less decrease in mean blood pressure than isoflurane¹⁹. This is supported by data for thiopentone and propofol, used either alone or in combination, in which no hypotension was reported but a decrease in blood pressure from baseline was observed^{21,27,28}. A decrease in mean blood pressure to below 60 mm Hg has been observed with administration of inhalational anaesthetic (isoflurane and halothane) following the induction of anaesthesia with propofol when only a small decrease in blood pressure was seen at induction⁴. What is evident from the literature is that propofol does decrease blood pressure from baseline levels in most studies but that the decrease in blood pressure was never to a level where hypotension was evident. TIVA should be should be given consideration in patients

where the maintenance of blood pressure is vital. However, further research is required before conclusive statements can be made.

The observation of a Cushing's reflex in Dog 4 is not a surprising finding, but underlies the importance of invasive blood pressure monitoring in these patients. Blood pressure rose sharply over a minute with an associated decrease in the heart rate. The treatment for this phenomenon is to decrease intracranial pressure. In this case, the Cushing's reflex was the result of manipulation of the central nervous system and was treated by stopping surgery until the blood pressure and heart rate had returned to normal. The diagnosis of the phenomenon may have been inhibited if cuff blood pressures had been used. The improved haemodynamic control may have been a consequence of the balanced anaesthesia used in these patients (propofol and morphine)¹⁵. The use of balanced anaesthesia should always be considered in compromised patients¹⁵.

The control of intracranial pressure is vital to a successful outcome following brain surgery. A number of techniques to control intracranial pressure have been proposed⁷. These techniques include hyperventilation, administration of mannitol and corticosteroid use. The induction of hyperventilation reduces the arterial partial pressure of carbon dioxide that leads to a decrease in cerebral blood volume and hence reduces intracranial blood pressure⁷. The decrease in cerebral blood volume is associated with a decrease in cerebral blood flow and the potential for an increased risk of ischaemic hypoxia⁷. The effect of hyperventilation on cerebral blood volume is not maintained and decreases with time⁷. The intention of ventilatory management in these patients should be to prevent an increase in the arterial partial pressure of carbon dioxide that may be catastrophic to intracranial blood pressure⁷. Hyperventilation was used in Dog 4 to control brain oedema until other pharmacological interventions had sufficient time to become effective. The evaluation of brain oedema is easy once the cranium has been opened and absence of brain pulsation should guide therapy.

The pre-operative administration of dexamethasone reduces oedema formation associated with cerebral tumours⁷. Dogs in this study were placed on dexamethasone before surgery. Dexamethasone changes the viscoelastic properties of the brain, allowing for better accommodation of changes in intracranial pressure, reduced oedema formation and improved clinical condition of the patient⁷. Steroid therapy

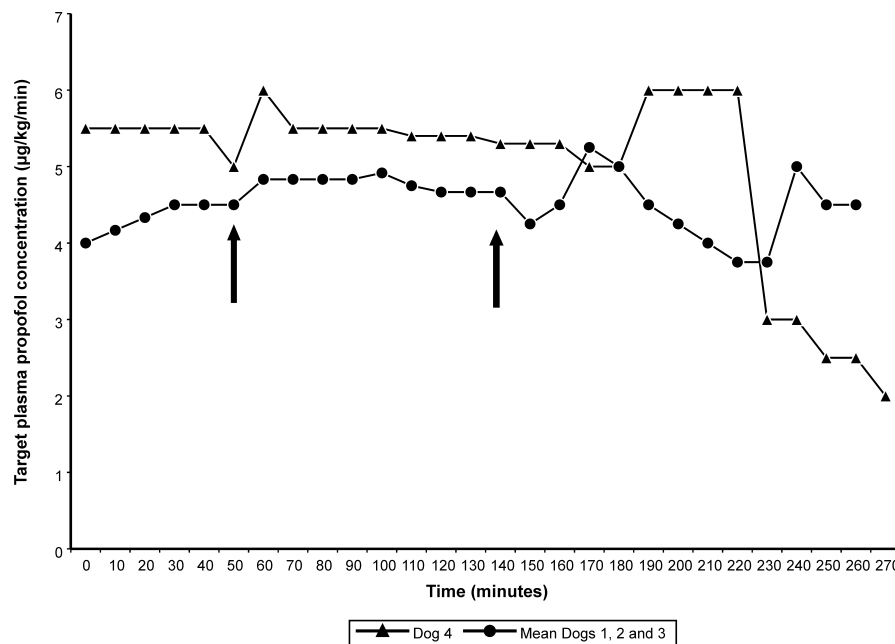


Fig. 2: Target blood propofol concentrations. The 2 arrows indicate the common surgical period for Dogs 1, 2 and 3. This period was used to determine the target concentration for Dog 4.

was maintained into the post-operative period. Mannitol was used to control intracranial pressure and brain oedema based on physical evaluation of the brain after the cranium was opened.

The fluid used in neurosurgery should not decrease the serum osmolarity while maintaining intravascular volume⁷. Normal saline is considered the fluid of choice as it is slightly hyperosmolar (308 mOsm/l)⁷. Blood loss can be rapid during neurosurgical procedures if a venous sinus is damaged. Such blood loss required the administration of fluids and blood to maintain circulating volume in 2 dogs. Rapid administration of fluids may increase the central venous pressure. A rise in central venous pressure is associated with an increase in intracranial pressure. Central venous pressure should be optimised and prevented from rising during surgery⁷. Positional changes can also cause changes in central venous pressure. The monitoring of central venous pressure is simple and should be utilised in all patients.

The use of Stelpump has not been documented in clinical veterinary anaesthesia. The program ran on a laptop computer and was connected to a syringe driver through an RS232 cable. It was found to be reliable and safe for the delivery of anaesthesia. The only system crash occurred because of an operator error when refilling a syringe with propofol at the end of the surgery in Dog 4. If the system does crash, the pharmacokinetic data stored in the program is no longer available and the program starts over again without knowledge of the current

predicated plasma concentration. This is a potential disadvantage of this system, as it will administer a bolus dose to achieve the targeted plasma concentration. Part of this study was undertaken to determine the suitability of the computer program with the pharmacokinetic data set determined by Beths *et al.* The plasma concentration shown in Fig. 2 is based on the predicted plasma concentration of the computer model. The predicted plasma concentrations may have no bearing on the actual plasma concentrations. Further evaluation of this system would require the determination of median performance error and median absolute performance error before further clinical application could be considered^{6,25}.

The emission of the volatile anaesthetic agents, halothane, isoflurane and enflurane, into the atmosphere will be prohibited in the year 2030²⁴. With the potential disappearance of inhalational anaesthetics, the development and refinement of TIVA techniques is vital to the successful practice of anaesthesia. The future research in TIVA should be directed towards establishing its role within veterinary anaesthesia. TIVA may have certain advantages to inhalational anaesthesia that includes better cardiovascular stability. The complexity of its administration though, may make it less suitable for routine cases.

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