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Is target-controlled infusion better than manual controlled infusion during TIVA for elective neurosurgery? Results of a single-centre pilot study

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ABSTRACT

Introduction. Maintaining optimal systemic circulatory parameters is essential to ensure adequate cerebral perfusion (CPP) during neurosurgery, especially when autoregulation is impaired.

Aim of study. To compare two types of total intravenous anaesthesia i.e. target controlled infusion (TCI) and manually controlled infusion (MCI) with propofol and remifentanil in terms of their control of cardiovascular parameters during neurosurgical resection of intracranial pathology.

Material and methods. Patients with supratentorial intracranial pathology were selected for the study. Patients in ASA grades III and IV and those with diseases of the circulatory system were excluded. Patients were randomly divided into two equal groups according to the method of general anaesthesia used i.e. TCI or MCI. During the neurosurgery, the values of mean arterial pressure (MAP), heart rate (HR), bispectral index (BIS) and central venous pressure were monitored and recorded at the designated 14 relevant (i.e. critical from the anaesthetist's and neurosurgeon's points of view) measurement points.

Results. Fifty patients (25 TCI and 25 MCI) were enrolled in the study. The groups did not differ with respect to sex, age and BMI, operation time or volume of removed lesions. TCI-anaesthetised patients had better MAP stability at the respective time points.

Conclusions. Due to the greater stability of MAP, which has a direct effect on CPP, TCI appears to be the method of choice in anaesthesia for intracranial surgery.

Keywords: total intravenous anaesthesia (TIVA), target controlled infusion (TCI), manually controlled infusion (MCI), mean arterial pressure (MAP), neurosurgery

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Introduction

In neurosurgical anaesthesia, haemodynamic stability is important, because the value of mean arterial pressure (MAP) is one of the most important factors that correlates with cerebral perfusion pressure (CPP). High variability of MAP is therefore a prognostically unfavourable factor [1–4]. According to some authors, total intravenous anaesthesia (TIVA) in neurosurgery provides less fluctuation in MAP compared to complex anaesthesia, and therefore causes less fluctuation in CPP when intracranial pathology causes cerebral autoregulation disorders [5, 6]. Total intravenous anaesthesia can be performed using one of two methods, either manual controlled infusion (MCI) or target controlled infusion (TCI) [7]. The terms MCI and TCI refer to two different approaches to administering intravenous anaesthesia. These techniques are used to control the delivery of anaesthetic drugs to maintain the desired level of anaesthesia during neurosurgery.

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In MCI, an anaesthesiologist manually adjusts the infusion rate of anaesthetic drugs based on clinical observations and the patient's responses [7–10].

TCI involves the use of a computerised infusion system that calculates and controls the rate of drug administration to achieve and maintain a target concentration of the anaesthetic drug in the patient's blood [11–13].

In the present study, we set out to find out which technique of TIVA, MCI or TCI, provides greater haemodynamic stability, and therefore CPP, during anaesthesia for elective neurosurgery of supratentorial pathology.

Material and methods

Eligibility criteria for study

This study was conducted on a group of 50 patients hospitalised at the Neurosurgery Clinic of the University Clinical Centre in Gdańsk, Poland. Included in the study were patients with intracranial pathologies who underwent elective craniotomy with removal of the lesion under general anaesthesia. Excluded from the study were patients presenting comorbidities classified as ASA III/IV, those with cardiac disease (e.g. atrial fibrillation and other arrhythmias, poorly controlled hypertension), substance abuse, and alcohol dependence. Patients presenting what are called 'difficult airways' were also disqualified. Depending on the anaesthesia method used, patients were randomly divided into two equal groups:

- Manually controlled infusion (MCI);
- Target controlled infusion (TCI).

Block randomisation was used to determine allocation to each group.

Course of study

In the operating room, before the induction of anaesthesia, a cannula (Vasofix Safety, B. Braun, Melsungen, Germany) was placed into a vein on the dorsal part of the hand. ECG monitoring was started, and blood pressure, transcutaneous arterial haemoglobin saturation, capnography, and BIS were measured.

Preoxygenation was performed, followed by the induction of total intravenous anaesthesia (TIVA) using the MCI or the TCI method. The remifentanil (Ultiva, Aspen Pharma, Umhlanga, South Africa) and propofol (Propofol 1% MCT/LCT, Fresenius, Bad Homburg, Germany) infusion was performed using a Perfusor Space infusion pump (B. Braun, Melsungen, Germany).

In the P-TCI group, the procedure started with entering the patient's demographic data (height, gender, weight, and age), and setting the initial target concentration at the effect site at 4 μg/mL for propofol in the Schnider model, and at 4 ng/mL for remifentanil in the Minto model.

Meanwhile in the P-MCI group, the procedure started with the administration of a bolus of propofol at a dose of 1.5 mg/kg IBW and remifentanil at a dose of 0.5 μg/kg IBW for one minute.

Subsequently after the induction dose, continuous infusion using infusion pumps was started. The initial dose was set at 3–6 mg/kg/h for propofol and at 0.1 μg/kg/min for remifentanil. The infusion rate was adjusted depending on the current values of haemodynamic parameters, including heart rate, mean arterial pressure, and BIS.

After loss of consciousness and disappearance of the eyelash reflex, face mask ventilation was initiated. When the BIS value dropped below 60, measurement of the degree of neuromuscular blockade (TOF-watch) was started. Rocuronium (Rocuronium Kabi, Fresenius, Bad Homburg, Germany) was administered as a bolus at a dose of 0.6 mg/kg of ideal body weight, and then continuous infusion was maintained at a dose of 0.6 mg/kg/h. When the response of the adductor pollicis (thumb) muscle to TOF stimulation (TOFWatch SX, Organon, Ireland) disappeared, endotracheal intubation was performed. During the maintenance of anaesthesia, the propofol infusion was adjusted to the BIS value in the range of 35–60. If it was necessary to modify the dose, the propofol infusion rate was increased or decreased by 1 mg/kg/h^{-1} in the P-MCI group. In the P-TCI group, the target concentration of propofol was increased or decreased by 1 μg/mL.

The remifentanil infusion dose was modified depending on the heart rate and blood pressure parameters to achieve maximum haemodynamic stability compared to the initial values. If necessary, the remifentanil infusion rate was changed in the P-MCI group by 0.05 μg/kg/min, and in the P-TCI group, the target remifentanil concentration was modified by 1 ng/mL.

A central catheter (Certofix TrioV715, Melsungen, Germany) was inserted into the internal jugular vein and central venous pressure (CVP) was measured.

A cannula (arterial cannula, Becton Dickinson, Franklin Lakes, NJ, USA) was inserted into the radial artery and a direct blood pressure measurement was started.

Both the neurosurgeons and the anaesthesiologists were experienced in performing craniotomy and anaesthesia for this type of procedure.

After intubation, a Primus anaesthetic machine (Dräger, Lübeck, Germany) was connected to the patient. Patients were ventilated with a mixture of oxygen and air with FiO2 0.4, tidal volume (VT) 4–6 mL/kg IBW in the IPPV mode. The respiratory rate was adjusted to the value of end-tidal carbon dioxide tension ($etCO_2$), which was maintained in the range of 30–40 mmHg, after having previously verified the difference between the end-tidal carbon dioxide value and its tension value in arterial blood.

Parameters under study

During the study, the values of selected parameters were monitored and recorded at 14 critical measurement points (for the anaesthesiologist and the neurosurgeon) before, during, and after the surgery and the anaesthesia. A measurement was made when the critical point occurred, and one minute later. In the central phase of operation, measurement points were

designated at the beginning, middle, and end of the central phase, typically when haemostasis was achieved.

During the study, the following data was taken into consideration:

- haemodynamic parameters: heart rate (HR); mean arterial pressure (MAP); central venous pressure (CVP)
- bispectral index value (BIS)
- set/read values of drugs administered from infusion pumps (propofol, remifentanil) depending on the method of anaesthesia

This study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk.

Statistical analysis

After examining the distributions of the analysed variables — MAP, HR, BIS, CVP — non-parametric tests were used for statistical analyses. Analyses of distribution were performed using the Shapiro-Wilk test. For within-group analyses of MAP, HR, BIS and CVP, the sign test (dependent variables) was used. For intergroup analyses of the above variables, the Mann-Whitney U test was used (variables in the intergroup analysis were treated as indipendent variables). Qualitative variables were analysed using the chi-square test, also with Yates's correction. Results are presented as means, medians and standard deviations. Results where $P < 0.05$ were considered statistically significant.

Results

Characteristics of patient groups

Basic data regarding the operated groups of patients is set out in Table 1.

There were no significant differences between the groups in the analysed parameters: demographics, BMI, operation time, or volume of removed lesions.

Table 2 shows the types of CNS pathology depending on their histopathological diagnosis and location. No significant differences were found between the P-TCI and the P-MCI groups.

Parameters monitored during anaesthesia

Heart rate (HR)

Statistical analysis did not show statistically significant differences in heart rate values at specific time points between both groups, while intra-group differences were noted for the following subsequent time points (Fig. 1A):

I. P-MCI group:

- between the average heart rate values at T_1 point — one minute after administration of the initial dose of propofol and remifentanil, and T_2 point — the moment when the muscle relaxant was administered, after propofol was administered, when the BIS value dropped below 60, ($p = 0.04$).

Table 1. Characteristics of patients in P-TCI and P-MCI groups (mean and standard deviation, median in brackets)

Group	P-TCI	P-MCI	p-value
Gender (W/M)	15/10	17/8	0.39
Age (years)	60.8 ± 14.6 (67.0)	55.08 ± 12.2 (56.0)	0.59
BMI (kg/m^2)	26.93 ± 3.7 (26.17)	26.62 ± 4.7 (26.67)	0.79
Surgery duration (min)	134.00 ± 57.48 (128)	136.16 ± 59.50 (126)	0.90
Volume of removed lesion (mL)	52.01 ± 50.96 (24.43)	56.93 ± 58.29 (23.43)	0.79

P-TCI — patients anaesthetised using TCI method. P-MCI — patients anaesthetised using MCI method

Table 2. Type of operated intracranial pathologies according to histopathological diagnosis and location

Type of intracranial pathology and location in CNS	P-TCI (n)	P-MCI (n)	All	p (chi-square Yates)
Meningioma	8	10	18	0.21
Glioblastoma	8	7	15	
Other glial tumour	3	4	7	
Metastases to brain	5	2	7	
Other	1	2	3	
Frontal lobe	11	10	21	0.93
Temporal lobe	10	10	20	
Parietal lobe	3	4	7	
Occipital lobe	1	1	2	

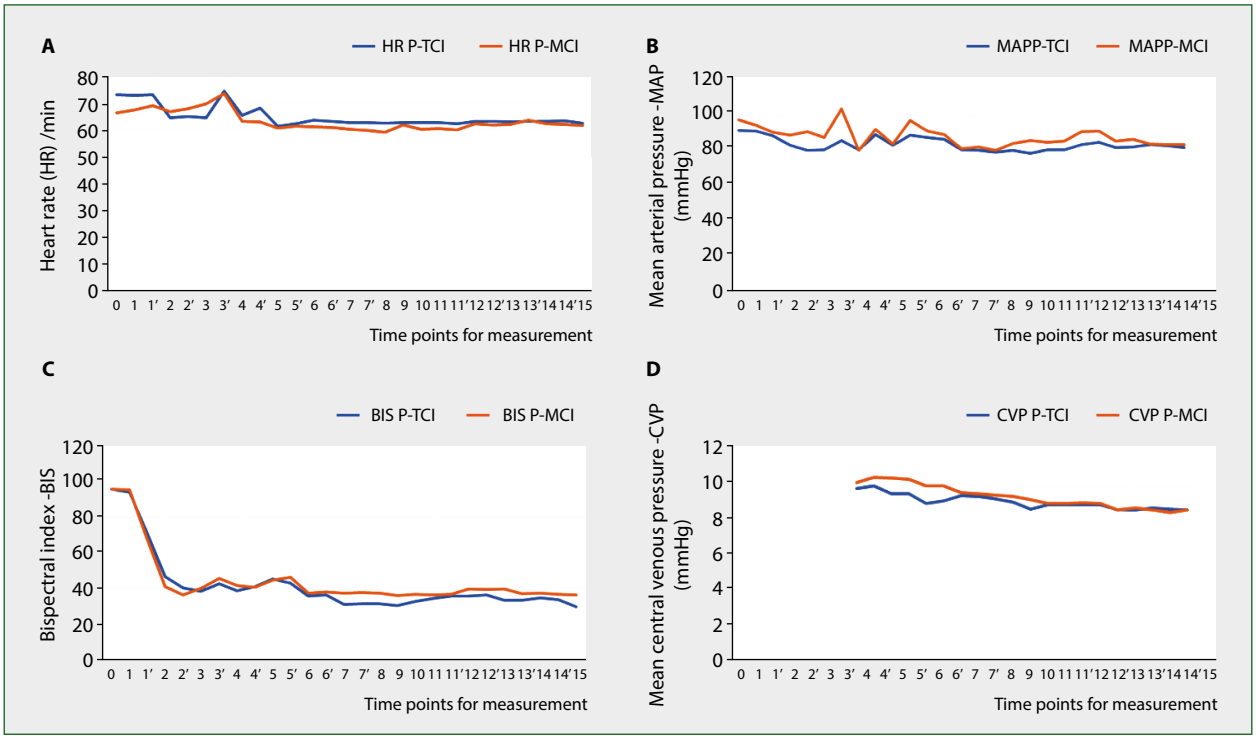

Figure 1. A. Heart rate changes during neurosurgery; **B**. Mean arterial pressure changes during neurosurgery; **C**. Bispectral Index changes during neurosurgery; **D**. Mean central venous pressure changes during neurosurgery

II. P-TCI group:
– between the average heart rate values in points:
  - $T_{1'}$ — one minute after administration of the initial dose of propofol and remifentanil, and T_2 point — the moment when the muscle relaxant was administered, after propofol was administered, when the BIS value dropped below 60 (p = 0.02);
  - $T_{3'}$ — one minute after endotracheal intubation, and T_4 point — head fixation in a head stabilising frame (p = 0.046);
  - $T_{4'}$ — one minute after head fixation in a head stabilising frame, and T_5 point — skin incision (p = 0.005).

Mean arterial pressure (MAP)

Statistical analysis regarding the measurement of mean arterial pressure showed statistically significant differences at specific time points between both groups (Fig. 1B):
– $T_{3'}$ — one minute after endotracheal intubation (p = 0.049);
– $T_{5'}$ — one minute after skin incision (p = 0.047);
– T_{10} — end of the central phase (p = 0.02);
– $T_{11'}$ — one minute after the start of dura mater closure (p = 0.045);
– T_{12} — start of bone closure (p = 0.023);
– $T_{12'}$ — one minute after the start of bone closure (p = 0.037).

There were also statistically significant intra-group differences between the mean arterial pressure (MAP) values at the following time points:

I. P-MCI group:
– in important/critical moments (points) of anaesthesia and surgery:
  - T_3 — enotracheal intubation, and $T_{3'}$ point –– one minute after enotracheal intubation (p = 0.002);
  - T_4 — head fixation in a head stabilising frame, $T_{4'}$ point — one minute after head fixation in a head stabilising frame (p = 0.02);
  - T_5 — skin incision, and $T_{5'}$ point — one minute after skin incision (p = 0.0002);
  - T_8 — start of the central phase, and T_9 point — middle of the central phase;
– in the periods between important/critical moments (points) of anaesthesia and surgery:
  - $T_{3'}$ — one minute after intubation and point T4 — start of the insertion of the headholder (the neurosurgical part in the operating theatre preparing the patient for the essential part for surgery) (p = 0.005);
  - $T_{6'}$ — one minute after the start of bone opening, and T_7 point — opening of the dura mater (p = 0,008);
  - $T_{11'}$ — one minute after the start of dura mater closure, and T_{12} point — start of bone closure;
  - $T_{12'}$ — one minute after the start of bone closure, and T_{13} point — start of soft tissue closure.

II. P — TCI group
– in important/critical moments (points) of anaesthesia and surgery:

- $T_{1'}$ — one minute after administration of the initial dose of propofol and remifentanil, and T_2 point — the moment when the muscle relaxant was administered, after propofol was administered, when the BIS value dropped below 60 (p = 0.016);

— in the periods between important/critical moments (points) of anaesthesia and surgery:

- $T_{6'}$ — one minute after the start of bone opening, and T_7 point — opening of the dura mater (p = 0.005);
- T_{10} — end of the central phase, a T_{11} point — start of dura mater closure (p = 0.012);
- $T_{12'}$ — one minute after the start of bone closure, and T_{13} point — onset of soft tissue closure (p = 0.02).

Bispectral index (BIS)

Both in the P-TCI patient group and in the P-MCI patient group, at subsequent time points, the bispectral index (BIS) values were lower compared to the initial value (Figure 1C).

The mean initial BIS value in both study groups was 96, while after the infusion of the initial dose of propofol during the induction of general anaesthesia (when the BIS value dropped below 60), in the P-TCI group the mean bispectral index value was 36 ± 10.1 (95% CI: 29.85–42.23). However, in the P-MCI group it was 39 ± 10.4 (95% CI: 34.07–43.31).

There was no significant statistical difference between the groups or within the groups at subsequent time points throughout the entire anaesthesia (except for the initial value),

Central venous pressure (CVP)

The mean values of central venous pressure in the P-TCI group were 9.06 ± 1.88 (95% CI: 8.28–9.84), and in the P-MCI group 9.37 ± 2.4 (95% CI: 8.38–10.36). There was no significant statistical difference between the groups or within the groups at subsequent time points (from point P4, after insertion of the central catheter) (Fig. 1D).

Discussion

The aim of this study was to compare the effects of two types of total intravenous anesthesia: the classical i.e. manually controlled infusion (MCI) and target-controlled infusion (TCI) using propofol and remifentanil on selected cardiovascular parameters (haemodynamic stability) in neurosurgical patients undergoing elective surgical resection of intracranial pathologies.

It is well known that during surgery of patients with intracranial pathologies, haemodynamic disturbances in arterial blood pressure and heart rate are particularly dangerous. When cerebral autoregulation is disrupted, unstable systemic circulation impacts upon cerebral circulation. Maintaining adequate systemic circulation is essential to ensure appropriate brain perfusion.

During the entire neurosurgical operation, values of heart rate and mean arterial pressure (MAP) were monitored and subjected to intragroup and intergroup statistical analysis at 14 critical measurement points. There could potentially be significant fluctuations in these haemodynamic parameters at these points.

At the same time, the values of central venous pressure (CVP) and bispectral index (BIS) were measured and statistically analysed during the entire procedure. This reduced the risk of false haemodynamic results due to hypovolemia or intraoperative awakening.

There were no statistically significant differences in the values of central venous pressure and bispectral index, either within or between the two groups.

Therefore, it must be concluded that both groups were homogeneous in this regard.

There was a statistically significant difference in MAP in the MCI group not only at the time of intubation (the strongest pain), but also at the time of applying the head stabiliser and the skin incision at the beginning of the operation. Importantly, this difference was not observed in the TCI group. An important moment during craniotomy is also the opening of the dura mater, where potential brain tissue swelling causes increased intracranial pressure [14]. In our study, no statistically significant haemodynamic differences were observed in both methods of anaesthesia in this phase of surgery, either within or between the groups.

There were no statistically significant differences during the further stages of the operation, including the central phase and the period of tissue closure at the end of the operation.

The obtained results allow us to conclude that haemodynamic stability in terms of MAP is higher when the TCI method is selected.

However, it should be noted that the type of anaesthesia did not affect the neurological condition of the patients (which was similar to the condition before the operation). Therefore, the greater variability of MAP in the MCI group did not result in a deterioration of patient conditions. This aspect of our observation requires further research on a much larger group of patients.

Comparing this study and its results to the available literature is not an easy task, since there are is little literature comparing both systems during anaesthesia of neurosurgical patients, especially in intracranial operations.

Wang X et al. showed that anaesthesia using TCI in patients undergoing functional epilepsy surgery in the AAA (Asleep-Awake-Asleep) protocol allowed for a significantly shorter time before awakening. This is an extremely valuable feature that is used especially in cerebral cortex surgeries during intraoperative awakening. In the TCI group, MAP and heart rate were more stable. Wang X et al. speculated that greater haemodynamic stability was achieved due to a more stable drug concentration in plasma [15].

Similarly, Ozkose et al. also demonstrated that the use of TIVA facilitates intraoperative awakening. The use of TCI for drug administration helps adjust drug concentrations in a desired, user-friendly manner that facilitates patient awakening [16].

Several studies have shown the advantage of using TCI during non-neurosurgical procedures. Wang JF et al. conducted a study on patients anaesthetised with both TCI and MCI for colonoscopy. In the TCI group, they observed greater MAP stability, and faster awakening of patients, but with lower peripheral oxygen saturation [17].

Müller et al. showed in their study that the time needed to wake up patients after laparoscopic gynaecological surgeries was shorter after TCI. Additionally, the frequency of nausea and vomiting was lower compared to the MCI method [18].

Chiang et al. also confirmed faster awakening with the TCI system [19]. Their study also showed more stable MAP values and a shorter period of bradypnoea and desaturation in patients undergoing sedation for ERCP and colonoscopy procedures.

According to Yeganeh et al., propofol and remifentanil infusion using total intravenous anaesthesia in a TCI system during mastoidectomy surgery showed greater haemodynamic stability, faster time to obtain 10 points on the Aldret score, and lower incidence of postoperative nausea and vomiting (PONV) [20].

Some studies have emphasised a more frequent unintentional return of consciousness in the case of total intravenous anaesthesia. Monitoring the bispectral index (BIS), which assesses the effect of anaesthetics on the cerebral cortex, may reduce the likelihood of consciousness return [21].

Nimmo et al. proved that the use of devices with the TCI system is associated with a lower probability of consciousness return during anaesthesia [22]. Our study did not show an advantage of the TCI system over the MCI method in this aspect. Similarly, in the study by Gale et al., anaesthesia in both the TCI and MCI systems allowed comparable depths of anaesthesia and BIS stability to be obtained [23].

In summary, target-controlled infusion seems to be the preferred method in craniotomy procedures due to greater haemodynamic stability in terms of mean arterial pressure (MAP). This stability directly impacts upon cerebral perfusion pressure (CPP) during critical moments of intracranial surgery, especially in patients with intracranial pathology.

Infusion of propofol and remifentanil using the TCI and MCI methods achieves and maintains a stable depth of anaesthesia.

Data availability statement: *The data that supports the findings of this study is available on request from the corresponding author.*

Ethics statement: *This study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk.*

Authors' contributions: *SN — study design, data collection, writing manuscript; KC — study design, statistical analysis, writing manuscript; RO — study design, writing manuscript*

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