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Bispectral index values and propofol concentrations at loss and return of consciousness in patients with frontal brain tumours and control patients

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Editor's key points

- Intracranial pathology may affect the accuracy and interpretation of bispectral index (BIS) monitoring.
- This study found no significant differences in BIS between tumour and control patients, nor between the affected hemisphere and the contralateral hemisphere.
- In patients with small frontal tumours, there is no need to alter propofol dosage or its titration according to BIS.
- The thresholds at which the extent and type of intracranial pathologies affect BIS are largely unknown.

Background. The influence of frontal brain tumours on bispectral index (BIS) measurements and propofol requirements is unknown. The primary aim of our study was to determine whether BIS values recorded at loss and return of consciousness (LOC and ROC, respectively) differ between patients with unilateral frontal brain tumours and control patients. Secondary goals were to compare propofol requirements for LOC and to determine whether there were significant inter-hemispheric differences between BIS values in tumour and control patients.

Methods. We enrolled 20 patients with a frontal brain tumour and 20 control patients. Bilateral BIS measurements were done during induction of propofol anaesthesia, during recovery of consciousness, and during a second induction of anaesthesia. The isolated-forearm test was used to determine the moments of LOC1, ROC, and LOC2. Arterial blood samples were obtained every 4 min for determination of measured propofol concentrations.

Results. The median BIS values recorded at LOC1, ROC, and LOC2 did not differ between the groups. There were no significant inter-hemispheric differences in BIS in tumour and control patients. The median [inter-quartile range (IQR)] total propofol doses at LOC1 were 82 (75–92) and 78 (68–91) mg in tumour and control patients, respectively. The median (IQR) measured plasma propofol concentrations at LOC1 were 12 (9–14) and 13 (11–15) $\mu g\ ml^{-1}$ in the tumour and control groups, respectively.

Conclusions. The presence of a frontal brain tumour did not affect ipsilateral BIS values, and so need not influence the placement of unilateral BIS electrodes if BIS monitoring is used to titrate propofol anaesthesia.

Keywords: brain tumour; depth of anaesthesia; monitoring, bispectral index; pharmacology, propofol

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Many anaesthetists measure and record the bispectral index (BIS) (Bispectral Index, Covidien, Boulder, CO, USA) during craniotomy for excision of brain tumours, and use the BIS to guide titration of the anaesthetic agents. However, there have been few studies investigating the influence of brain tumours on the reliability of the BIS as a measure of hypnosis. As far as we know, no studies have specifically addressed the issue of the influence of *frontal* brain tumours on the relationship between the BIS and conscious state.

One study, involving 13 patients with small supra- and infratentorial tumours, and 13 control patients, was designed to evaluate the relationship between estimated effect-site concentrations and the BIS during loss of consciousness (LOC).[1] For induction of anaesthesia, propofol was administered at a rate of 2000 mg h^{-1} in all patients, but achieved plasma concentrations were not measured. Although the authors found significantly *higher* overall BIS values over time in tumour patients during the induction, and *higher* BIS values for estimated effect-site concentrations >2.5 $\mu g\ ml^{-1}$, there were no statistically significant differences in BIS and propofol concentrations at LOC. Overall, the findings were inconclusive, difficult to interpret, and limited by the small sample size and by the inclusion of patients with non-frontal brain tumours.

† M.M.S. and U.B. contributed equally to this study and should both be considered first author.

It is a common perception among anaesthetists that patients with brain tumours are sensitive to the effects of commonly used anaesthetic agents, such as propofol, and accordingly they administer cautious induction doses. This practice, recommended in some textbooks,[2] is chiefly supported by clinical experience, expert opinion, and by one small study which did indeed show evidence that propofol requirements are decreased in patients with large supratentorial brain tumours.[3] During neurosurgery, propofol-based total i.v. anaesthesia is commonly practiced, with the propofol often administered by target-controlled infusion (TCI). If there are pharmacokinetic, pharmacodynamic, or both differences among patients with tumours, then the models which are used for TCI propofol may be inaccurate in these patients.

Overall, it remains unclear whether anaesthetic dose-titration according to the BIS is advisable in patients with cranial tumours, and whether or not these patients are more susceptible to the hypnotic effects of propofol. The primary aim of our prospective observational study was to compare BIS values recorded at LOC and ROC among patients with unilateral frontal brain tumours and patients with no brain tumour. Secondary goals were to determine whether there were differences between BIS values recorded on the ipsilateral and contralateral hemispheres in tumour patients, and to compare propofol dose and measured plasma concentration requirements for LOC in these two patient groups.

Methods

Clinical protocol

After institutional ethics committee approval (UMCG ethics committee, number 2009058) and registration at ClinicalTrials.gov (NCT01060631), we obtained informed consent from 53 ASA I–III patients older than 18 yr of age for inclusion in the study. The study group comprised 24 patients with a known frontal intracranial tumour proven by a recently obtained magnetic resonance imaging (MRI) image, who were undergoing an elective tumour excision. Patients were prospectively assessed for the presence of significant neurological deficits. Those with any sensorimotor or cognitive deficits that may have interfered with assessments of consciousness were not considered eligible for the study. For MRI images, see Figure 1. The control group comprised 29 patients without intracranial pathology planned to undergo an elective spinal neurosurgical operation. Exclusion criteria for both groups were any conditions or treatments that could potentially interfere with respiratory or cardiovascular status of the patient during the study. Complete group allocation is reported in Figure 2.

The study was performed before any surgical intervention in a quiet operating theatre, with the following personnel present: one coordinating researcher, one anaesthetist responsible for the safety and anaesthetic care of the patient, one anaesthetic nurse, and a second anaesthetist responsible for blood sampling and other tasks.

On arrival in the operating theatre, an i.v. cannula was inserted in the non-dominant hand or forearm. All patients received an i.v. infusion of crystalloid solution, at a rate of 500 ml h^{-1}, to deliver the required drugs and fluids during the study period. After the placement of routine cardiovascular and respiratory monitors, an intra-arterial catheter was inserted under topical anaesthesia in the non-dominant radial artery and connected to a pressure transducer. Bilateral BIS electrodes were placed as recommended by the manufacturer and bilateral BIS and bilateral frontal electro-encephalographic activity was recorded using a Vista monitor (Covidien) with seven electrodes. Heart rate, three-lead ECG, capnography, and pulse oximetry and invasive arterial pressure were also recorded continuously using a Philips IntelliVue MP50 (Philips, Eindhoven, The Netherlands) monitor. Numerical and waveform data were recorded electronically using Rugloop II © software (Demed, Temse, Belgium). The raw electroencephalogram was digitized at a rate of 128 Hz and stored for *post hoc* analysis.

The timeline of the study is shown in Figure 3. Anaesthesia was induced with continuous i.v. infusion of propofol 2% at a rate of 100 ml h^{-1}. During induction of anaesthesia, patients were verbally prompted every 10 s to squeeze the dominant hand. For the verbal commands, an electronic recording was relayed to the patient by headphones using Microsoft Windows Media Player at maximum volume. The coordinating researcher remained at the patient's dominant side and could hear the auditory commands. The observer informed the other investigators of LOC at the time of the second failure of the patient to respond to the verbal command. The following were then performed as soon as possible: the time of the loss of response was recorded electronically (by free text entry in RUGLOOP) and on paper, the estimated effect-site concentration at LOC1 was noted, the first arterial blood sample was withdrawn and the time of withdrawal of the sample recorded, the fixed rate propofol infusion was stopped, and an effect-site TCI propofol infusion was begun with the target concentration set to that noted at LOC1.

To improve the quality of EEG signals and BIS registration, rocuronium bromide (Fresenius-Kabi, France) was administered and a laryngeal mask airway (LMA) was inserted in order to maintain a patent airway. To facilitate registration of subsequent responses to commands, the isolated forearm technique was applied. Thus, before administration of rocuronium, a padded tourniquet was applied to the dominant upper arm and inflated 20% above the systolic arterial pressure.

At 15 min after LOC1, a noxious stimulus in the form of a 30 s electrical tetanic stimulus (100 Hz, 60 mA) was applied to the dominant forearm. At 20 min after LOC, the propofol TCI target was set to zero (thereby stopping the infusion) and patients were again verbally prompted every 10 s to squeeze the dominant hand. The second subsequent purposeful response to this prompt was noted as return of consciousness (ROC), the time was noted, and the propofol infusion was restarted at 100 ml h^{-1} until the response ceased and the patient lost consciousness for the second time (LOC2). This signalled the end of the study and further preparation for surgical procedure was commenced as planned.

Propofol infusions were administered by Orchestra DPS infusion pumps (Fresenius-Kabi) controlled by the RUGLOOP II