BMJ Open

Effect of anesthesia *de*pth on *p*ostoperative clinical ou*t*come in patients with supratentorial tumor (DEPTH): study protocol for a randomized controlled trial

Qianyu Cui, Yuming Peng, Xiaoyuan Liu, Bo Jia, Jia Dong, Ruquan Han

To cite: Cui Q, Peng Y, Liu X, *et al*. Effect of anesthesia *de*pth on *p*ostoperative clinical ou*t*come in patients with supratentorial tumor (DEPTH): study protocol for a randomized controlled trial. *BMJ Open* 2017;**7**:e016521. doi:10.1136/bmjopen-2017-016521

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-016521).

Received 20 February 2017
Revised 19 May 2017
Accepted 19 June 2017

Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Correspondence to
Dr Ruquan Han;
ruquan.han@gmail.com

ABSTRACT

Introduction Recent studies have shown that deep anaesthesia is associated with poor outcomes. However, no randomised controlled trials have been conducted to test the causality in patients undergoing brain tumour resection.

Methods and analysis DEPTH is a multicenter, randomised, parallel-group, blind trial. The depth of general anaesthesia will be monitored using the bispectral index (BIS). Patients elected for supratentorial tumour resection will be randomly allocated to the deep or the light anaesthesia group in which the target BIS value is 35 or 50, respectively. BIS will be maintained at the target value for more than 90% of the total anaesthesia period. The primary outcome is the disability-free survival rate at postoperative 30 days and 1 year. The secondary outcomes are the mortality and morbidity within 30 days after surgery.

Ethics approval and dissemination Ethical approval has been granted by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medicine University. The reference number is KY2016-059-02. The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Trial registration NCT03033693.

Strengths and limitations of this study

- To date, DEPTH is the first randomised controlled trial to test the causal relationship between anaesthesia depth and postoperative outcomes in patients undergoing supratentorial tumour surgery.
- There are nearly six thousand cases of supratentorial tumour every year at Beijing Tiantan Hospital, Capital Medical University. It is feasible and reasonable to complete the trial with a large sample size in 3 years.
- This study is not a double-blind study. It is not practical for the anesthesiologists to be blinded to the grouping. However, the patients and the outcome assessors will be blinded to anaesthesia depth.
- There is no conclusive information about BIS monitoring in patients with supratentorial brain tumours undergoing craniotomy, which will be the secondary analysis of DEPTH.

BACKGROUND

A recent study shows that the average incidence of intracranial tumours in China is approximately twenty-five per hundred thousand,[1] most of which are supratentorial tumours. The clinical outcomes are very poor, placing a tremendous burden on families and society.[2] Therefore, increased perioperative attention is being paid to ways to increase the disability-free survival rate in patients undergoing brain tumour resection.

There are many factors associated with the survival of patients undergoing supratentorial tumour resection. Age, histologic type, the presence of seizures, tumour volume, and Karnofsky performance status (KPS) score have been confirmed as associated with overall and cause-specific survival.[3] Haydon *et al*[4] indicated that total resection improved the recurrence-free outcome and increased the postoperative survival rate. Soliman *et al*[5] showed that continuous intraoperative infusion of dexmedetomidine improved clinical outcomes in patients undergoing craniotomy. The anaesthesia method also affected the postoperative clinical outcomes.[6] However, there is still a lack of evidence regarding the association between anaesthesia depth and the postoperative clinical outcome in patients undergoing supratentorial tumour surgery.

Anaesthesia depth is defined as the degree of drug-induced non-responsiveness to stimulation under general anaesthesia.[7] The bispectral index (BIS), which is calculated from the original electroencephalography (EEG), is widely used to measure the depth of anaesthesia.[8–11] The BIS value ranges between 0 and 100, which represent burst suppression

and full awakeness, respectively. Watson *et al*[12] found a higher long-term mortality for patients who showed EEG burst suppression compared with those who did not (59% vs. 33%) during sedation in an intensive care unit (ICU). Chan[13] and colleagues showed that BIS-guided anaesthesia decreased the risk of postoperative cognitive dysfunction (POCD) at 3 months. Recent studies have suggested that deeper anaesthesia was associated with worse outcomes in surgical patients.[12 14–16] However, there are no such studies involving patients with supratentorial tumours.

Under deep anaesthesia, the circulatory system is inhibited; hence, cerebral blood flow, cerebral perfusion, brain electric activity, and energy metabolism are reduced.[17] The HR of postoperative mortality was 1.29 in patients with a persistent low BIS. When a BIS lower than 45 was maintained for an hour, the risk of death increased by 29%.[18] Leslie *et al*[19] found similar results. Monk *et al*[20] showed that the cumulative time of deep hypnosis and intraoperative hypotension were independent predictors of mortality. However, Sessler DI *et al*[21] performed a study of the depth of anaesthesia in 24 120 patients undergoing non-cardiac surgery that indicated that low BIS was not the only risk factor associated with high postoperative mortality. Willingham *et al*[22] indicated that intraoperative EEG suppression was a predictor of postoperative mortality only if mean arterial pressure (MAP) was also low. The postoperative 30 day mortality doubled when both low MAP and a low minimum alveolar concentration (MAC) were present.[21] However, targeting anaesthesia depth[23] at a specific BIS threshold did not decrease postoperative mortality.

There is still a lack of randomised controlled trials with a large sample size examining the effect of anaesthesia depth on postoperative outcomes in patients undergoing supratentorial tumour surgery. Based on the current literature, we propose the hypothesis that compared with light anaesthesia, deep anaesthesia leads to worse clinical outcomes in these patients. The disability-free survival rate at postoperative 30 days and 1 year will be the primary outcome. A randomised controlled trial will be designed to test this hypothesis.

METHODS

Study design

DEPTH is a multicenter, randomised, parallel-group, blind trial. The data will be collected from consecutive patients admitted to neurosurgery wards.

Objectives

The aim of DEPTH is to determine whether there is a causal relationship between anaesthesia depth and postoperative clinical outcome in patients undergoing supratentorial tumour surgery.

Inclusion criteria

Patients scheduled to undergo elective supratentorial tumour resection under general anaesthesia from 2017 to 2019 will be recruited for the trial. The inclusion criteria include age between 18 and 80 years, American Society of Anesthesiologists (ASA) physical status III-IV, surgery duration expected to be 3 hours or longer, postoperative hospital stay expected to be five nights or longer, and BIS monitoring throughout anaesthesia.

Exclusion criteria

Patients who undergo emergency or awake craniotomy surgery or are unable to provide written consent will be excluded from the trial. Patients whose incision site conflicts with the placement of BIS electrodes on the frontal and temporal lobes will also be excluded from the study.

Randomization and blinding

Permuted randomization will be used and stratified by age (older or younger than 50 years). Patients who meet the criteria will be randomly allocated to the deep group (BIS=35) or the light group (BIS=50). The distribution ratio will be 1:1. The anesthesiologists will not be blinded to the grouping. However, the patients and the outcome assessors will be blinded to the intervention.

Grouping

Based on the depth of anaesthesia monitored by BIS (BIS Complete Monitoring System; Coviden Ireland Limited, Dublin, Ireland), the patients will be randomly divided into the deep group or the light group, in which the BIS value will be targeted at 35 or 50, respectively. Research assistants will generate the allocation sequence and assign the participants to interventions. The anaesthesia depth in the deep group will begin to be adjusted when the BIS equals 32 or 38; in the light group, the anaesthesia depth will be adjusted when the BIS is 47 or 53. In this way, BIS will be maintained at no more than five units outside the targeted range for more than 5 min. The target BIS value will be maintained for 90% of the total time from the induction to the cessation of anaesthesia.

Anaesthesia induction and management

Standard routine monitoring will be instituted, including non-invasive blood pressure (NBP), electrocardiography (ECG), pulse oxygen saturation (SPO_2), end-tidal carbon dioxide PaO2 ($ETCO_2$), BIS, body temperature, continuous arterial pressure and urine output. All patients will be premedicated with midazolam 0.05 mg/kg intravenously. Total intravenous anaesthesia (TIVA) will be performed for all patients undergoing supratentorial tumour resections. No inhalational agent will be used. Ketamine and dexmedetomidine will not be used in DEPTH. Anaesthesia will be induced with sufentanil, rocuronium or cisatracurium and propofol or etomidate. After tracheal intubation, mechanical ventilation will be performed with a tidal volume of 8–10 mL/kg, a respiratory rate of 12–15/min, an inspiration and expiration ratio of 1:2, a fraction of inhaled fresh gas of 60% and a flow rate of fresh gas of 1–2 L/min to maintain normocapnia. Anaesthesia will

be maintained with intravenous propofol and remifentanil and supplemented with intravenous rocuronium or cisatracurium for muscle relaxation. Sufentanil will be administered to attenuate potent stress responses induced by noxious stimuli at certain time points during skull opening, such as scalp incision and skull drilling. Crystalloid infusion and colloid infusion will be used as needed. The comorbidities, the dosage of anaesthetic drugs, and the physical parameters will be recorded. Fluid input and output will also be closely monitored and recorded.

At the end of the surgery, ondansetron will be administered to prevent postoperative nausea and vomiting. Neostigmine and atropine will be used to antagonise remnant muscle relaxation. Postoperative patient-controlled intravenous analgesia (PCIA) formulation will be set as sufentanil (1–2 µg/kg) combined with ondansetron (16 mg) diluted to a total volume of 100 mL in 0.9% saline. The PCIA device provides a basal infusion of 2 mL/h and a bolus (0.5 mL, 15 min lock-out time). The patient will be delivered to the post-anaesthesia care unit (PACU) after the surgery.

Blood pressure management

The blood pressure will be maintained at the target value during the surgery. The baseline value is defined as the average MAP of the first three values measured after the patient enters operating room and before induction. The target value is defined as the range from below 15% to more than 20% of the baseline value. Blood pressure will be measured at 3 min intervals. When MAP is outside the target range, measures will be taken including adjusting the infusion rate of remifentanil and administering sufentanil and vasoactive agents (such as phenylephrine, norepinephrine and perdipine). The initial doses of norepinephrine and phenylephrine will be 0.01 µg/kg/min and 0.5 µg/kg/min, respectively.

Conversion between the groups

Anaesthesia will be deepened if body movement or intraoperative bucking occurs to ensure the safety of patients when the BIS value cannot be maintained within the target range anymore. If the intraoperative MAP is difficult to maintain within the target range after the standard operational procedure, the depth of anaesthesia will also be changed. The decision to convert will be made by the chief investigator for each medical centre, and the reason will be recorded.

Primary outcome

The primary outcome is the disability-free survival rate at postoperative 30 days. The WHO Disability Assessment Schedule 2.0 Scale (WHODAS 2.0) will be used to assess the disability before surgery and 30 days and 3 months after surgery.[24] Disability is defined as a 4-point reduction in the WHODAS score.

Secondary outcomes

- Outcome assessment will be conducted by research members who have been trained before the study and are blinded to the grouping.
- Intraoperative awareness: the modified Brice questionnaire[25–27] will be administered to assess intraoperative awareness at 1 day and 30 days after surgery.
- Postoperative delirium: the Confusion Assessment Method for the Intensive Care Unit scale (CAM-ICU) will be applied to assess postoperative delirium within 1 day in the PACU or the ICU.
- Postoperative cognitive dysfunction: The Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and cognitive function assessment scale for dementia will be used 1 day before and 30 days after surgery to evaluate cognitive function.
- Recovery quality: the postoperative Quality of Recovery-15 score (QoR-15) will be applied to assess the quality of awakeness in the PACU.
- All-cause mortality: the incidence and the reason for mortality will be recorded at 30 days.
- The incidence of comorbidity will be recorded within the first three and 30 days after surgery. Morbidity[28] includes the incidence of myocardial infarction, cardiac arrest, pulmonary embolism, stroke, sepsis, surgical site infection and persistent postoperative pain.
- The progression-free survival rate and the survival rate at postoperative 1 year will be assessed.

Sample size calculation

Based on the previous literature,[29–31] we estimate that the disability-free survival rate at 30 days after surgery is approximately 80%, and we expect the survival rate of the patients in the light anaesthesia group to increase by 5%. We estimate that 2504 participants would provide 90% power to detect a 5% difference (80% vs. 85%) in the disability-free survival rate using a two-tailed alpha of 0.05.[32] Considering a drop-out rate of 20%, the total sample size was calculated as 3004.

Statistical plan

SPSS software (version 19.0) will be used for statistical analysis. The categorical data will be expressed as the number of patients (percentage) or median (IQR (IQR)) and analysed using chi-square tests or Fisher's exact test. The continuous data will be expressed as the mean ± SD and analysed using the Mann-Whitney U test or independent t test.

The disability-free survival rate at postoperative 30 days and 3 months will be compared using the chi-square test. The progression-free survival rate and survival rate at postoperative 1 year will be compared through chi-square test. The incidence of myocardial infarction, cardiac arrest, stroke, pulmonary embolism, sepsis, surgical site infection, intraoperative awareness and persistent post-operative pain will be analysed using chi-square tests or Fisher's exact test. The QoR-15 score, CAM-ICU score, WHODAS

score, MMSE score, and cognitive function assessment scale for dementia score will be analysed by using the Mann-Whitney U test or independent t test.

Subgroup analysis will be performed for age, comorbidities, histological type of tumour, duration of anaesthesia, and resection degree. Multiple logistics regression will be applied to determine the influence of these confounding factors on the primary outcome. All analyses will be based on the intention-to-treat (ITT) and per-protocol (PP) principles. The final conclusion will be based on the ITT principle. A p-value less than 0.05 will be considered to have statistical significance.

The project will be monitored by a data monitoring committee (DMC) composed of specialists in ethics, anesthesiology, statistics, and methodology. When the follow-up visits of 1500 participants are completed (estimated to occur after 1 year of recruitment), the interim analysis will be conducted to evaluate the efficacy of the primary outcome. The p-value for the analysis will be set at $p<0.001$.

Adverse events

All adverse events will be monitored and recorded until they are resolved. Once any adverse event occurs, it will be immediately reported to the endpoint adjudication committee, which will determine the severity and causality of the adverse events. The chief investigator will be responsible for all adverse events reported. The incidence of adverse events will be summarised for each group and compared using the chi-square test or Fisher's exact test.

DISCUSSION

DEPTH is a large randomised, multicenter, parallel-group, blind trial aiming to test the hypothesis that light anaesthesia will increase the disability-free survival rate at 30 days after surgery in patients undergoing supratentorial tumour surgery. It is recommended that the BIS value be maintained between 40 and 60 during routine general anaesthesia. However, BIS monitoring is not a routine procedure in clinical work. When anaesthesia was conducted with the BIS value hidden from the anaesthetist, patients were commonly anaesthetised at BIS levels between 30 and 50.[33 34] Moreover, the BALANCED study (registration number: ACTRN12612000632897) is an ongoing randomised controlled trial that aims to observe the effect of anaesthesia depth on the outcome of patients undergoing major surgery[28]; in that study, the targeted BIS value of the light anaesthesia group is also targeted at 35. Data suggest that the longer the BIS value remains below 40, the higher the risk of mortality; however, at present, there is no conclusive evidence that deep anaesthesia is associated with poor clinical outcomes in patients undergoing supratentorial tumour resection. Based on the existing references and the BALANCED study, the ethics committee of Beijing Tiantan Hospital approved the target BIS value of 35 for the light anaesthesia group in the DEPTH study. The BALANCED study focused on the 1 year all-cause mortality in patients older than 60 years who were scheduled to undergo major surgery.

Many studies have proven that BIS can monitor the depth of anaesthesia during craniotomy.[35 36] However, during neurosurgery in particular, the recommended placement of electrodes sometimes conflicts with the incision site. BIS can alternatively be monitored at the occipital lobe when the neurosurgical incision is located on the frontal lobe.[37] However, the monitored BIS values in the frontal and occipital lobes differ in the same person. Therefore, it is not suitable to use these two different monitoring sites in the DEPTH study, in which BIS value is the main intervention. Consequently, patients whose surgery site conflicts with the BIS monitoring sites on the frontal and temporal lobes will be excluded from the study. There will be no alternative set-ups.

Anaesthesia depth also has an impact on the other outcomes in patients undergoing surgery. Myles *et al*[26] performed a study of intraoperative awareness during anaesthesia in 2463 patients that showed that BIS-guided anaesthesia reduced the risk of intraoperative awareness in patients undergoing general anaesthesia. Messina *et al*[38] found that higher doses of anaesthetics reduced the risk of awareness. Law *et al*[39] conducted a randomised controlled trial on the effect of anaesthesia depth on postoperative pain in 135 patients. There was no clinically useful analgesic effect in the deep anaesthesia regimen. However, Sahni *et al*[40] performed a prospective observational study and found that keeping the BIS at 45 to 40 throughout the anaesthesia resulted in better postoperative pain relief in patients undergoing laparoscopic cholecystectomy. Farag *et al*[41] reported less POCD in patients undergoing deep anaesthesia. Similarly, An *et al*[42] also indicated that deeper TIVA decreased the incidence of cognitive dysfunction during the early postoperative period. However, no study has examined the effect of anaesthesia depth on the incidence of awareness, POCD, and postoperative pain in patients undergoing supratentorial tumour resection. Hence, differences in intraoperative awareness, POCD, and postoperative pain between the different depths of anaesthesia will be the secondary outcomes of the DEPTH study.

In summary, DEPTH is a large randomised, multicenter, parallel-group, blind trial that aims to test the hypothesis that light anaesthesia will increase the disability-free survival rate at 30 days after surgery in patients undergoing supratentorial tumour surgery. If the results from the BALANCED and DEPTH studies, both of which have large sample sizes, are positive, they will provide strong evidence of the contribution of anaesthesia to the clinical outcomes in surgical patients.

Dissemination

The results of this study will be disseminated through a presentation at scientific conferences and a publication in scientific journals.

Timeline

The study will take approximately three years to complete enrollment and outcome assessment. The recruitment started on February 1, 2017. The completion date will be December 31, 2019.

Audits

The DMC will audit through regular interviews, letters or telephones. The DMC reserves the right to audit the recruitment of patients at any time. The auditing process will be independent from the investigators.

Amendments to the protocol

Amendments to the protocol will only be made by academic committee and with the approval of the Medical Ethics Committee, Beijing Tiantan Hospital, Capital Medical University. All modifications will be recorded. Any modifications will be applied to all subsequent patients, and the registration record will be updated.

Contributors QC and YP are co-first authors. QC was involved in conception and design, data collection and analysis, and manuscript writing. YP was involved in conception and design, data collection and analysis, and manuscript revision. XL was involved in conception and design, data collection, and manuscript revision. BJ and JD were involved in design and manuscript revision. RH was involved in conception and design, data analysis, and manuscript revision. All authors have read and approved the final manuscript.

Funding DEPTH is supported by the Clinical Medicine Development of Special Funding Support from the Beijing Municipal Administration of Hospitals (number: ZYLX201708) and the Capital Development Research Fund Project (number: 2016-1-20410).

Competing interests None declared.

Patient consent Patients who are eligible for the trial will be given the informed consent by a member of the research team. All patients will be given ample time to consider participation in the trial. The patients who agree to participate in DEPTH and sign the informed consent will be involved. A completed informed consent form is required for enrolment in the trial. The investigators must maintain the original signed consent form, as well as an additional copy of this form.

Ethics approval Ethical approval has been granted by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medicine University. The reference number is KY2016-059-02. Patients who are eligible for the trial will be given the informed consent form by a member of the research team. The patients who agree to participate in DEPTH and sign the informed consent will be included. The outcome results will not be discussed or presented outside the trial group unless authorized by medical ethics committee. Compensation for ancillary and post-trial care will be provided through funding.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The manuscript is a protocol for a randomized controlled trial, which does not include data.

REFERENCES

1. Jiang T, Tang GF, Lin Y, *et al*. Prevalence estimates for primary brain tumors in China: a multi-center cross-sectional study. *Chin Med J* 2011;124:2578–83.
2. Zhang G, Huang S, Zhang J, *et al*. Clinical outcome of gliosarcoma compared with glioblastoma multiforme: a clinical study in Chinese patients. *J Neurooncol* 2016;127:355–62.
3. Bauman G, Fisher B, Watling C, *et al*. Adult supratentorial low-grade glioma: long-term experience at a single institution. *Int J Radiat Oncol Biol Phys* 2009;75:1401–7.
4. Haydon DH, Dahiya S, Smyth MD, *et al*. Greater extent of resection improves ganglioglioma recurrence-free survival in children: a volumetric analysis. *Neurosurgery* 2014;75:37–42.
5. Soliman RN, Hassan AR, Rashwan AM, *et al*. Prospective, randomized study to assess the role of dexmedetomidine in patients with supratentorial tumors undergoing craniotomy under general anaesthesia. *Middle East J Anaesthesiol* 2011;21:325–34.
6. Peruzzi P, Bergese SD, Viloria A, *et al*. A retrospective cohort-matched comparison of conscious sedation versus general anesthesia for supratentorial glioma resection . *J Neurosurg* 2011;114:633–9.
7. Shafer SL, Stanski DR. Defining depth of anesthesia. *Handb Exp Pharmacol* 2008;182:409–23.
8. Liu Q, Chen YF, Fan SZ, *et al*. EEG artifacts reduction by multivariate empirical mode decomposition and multiscale entropy for monitoring depth of anaesthesia during surgery. *Med Biol Eng Comput* 2016;13.
9. Hajat Z, Ahmad N, Andrzejowski J. The role and limitations of EEG-based depth of anaesthesia monitoring in theatres and intensive care. *Anaesthesia* 2017;72(Suppl 1):38–47.
10. Leslie K, Short TG. Anesthetic depth and long-term survival: an update. *Can J Anaesth* 2016;63:233–40.
11. Smajic J, Praso M, Hodzic M, *et al*. Assessment of depth of anesthesia: PRST score versus bispectral index. *Med Arh* 2011;65:216–20.
12. Watson PL, Shintani AK, Tyson R, *et al*. Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality. *Crit Care Med* 2008;36:3171–7.
13. Chan MT, Cheng BC, Lee TM, *et al*. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013;25:33–42.
14. Abdelmalak BB, Bonilla A, Mascha EJ, *et al*. Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial. *Br J Anaesth* 2013;111:209–21.
15. Short TG, Leslie K, Campbell D, *et al*. A pilot study for a prospective, randomized, double-blind trial of the influence of anesthetic depth on long-term outcome. *Anesth Analg* 2014;118:981–6.
16. Brown CH, Azman AS, Gottschalk A, *et al*. Sedation depth during spinal anesthesia and survival in elderly patients undergoing hip fracture repair. *Anesth Analg* 2014;118:977–80.
17. Liu N, Chazot T, Mutter C, *et al*. Elevated burst suppression ratio: the possible role of hypoxemia. *Anesth Analg* 2006;103:1609–10.
18. Kertai MD, Pal N, Palanca BJ, *et al*. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-Unaware trial. *Anesthesiology* 2010;112:1116–27.
19. Leslie K, Myles PS, Forbes A, *et al*. The effect of bispectral index monitoring on long-term survival in the B-aware trial. *Anesth Analg* 2010;110:816–22.
20. Monk TG, Saini V, Weldon BC, *et al*. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005;100:4–10.
21. Sessler DI, Sigl JC, Kelley SD, *et al*. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012;116:1195–203.
22. Willingham M, Ben Abdallah A, Gradwohl S, *et al*. Association between intraoperative electroencephalographic suppression and postoperative mortality. *Br J Anaesth* 2014;113:1001–8.
23. Kertai MD, Palanca BJ, Pal N, *et al*. Bispectral index monitoring, duration of bispectral index below 45, patient risk factors, and intermediate-term mortality after noncardiac surgery in the B-Unaware trial. *Anesthesiology* 2011;114:545–56.
24. Ustün TB, Chatterji S, Kostanjsek N, *et al*. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ* 2010;88:815–23.
25. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. *Br J Anaesth* 1970;42:535–42.
26. Myles PS, Leslie K, McNeil J, *et al*. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet* 2004;363:1757–63.

27. Nordström O, Engström AM, Persson S, *et al*. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. *Acta Anaesthesiol Scand* 1997;41:978–84.
28. Short TG, Leslie K, Chan MT, *et al*. Rationale and design of the balanced anesthesia study: a prospective randomized clinical trial of two levels of anesthetic depth on patient outcome after major surgery. *Anesth Analg* 2015;121:357–65.
29. Barnholtz-Sloan JS, Sloan AE, Schwartz AG. Relative survival rates and patterns of diagnosis analyzed by time period for individuals with primary malignant brain tumor, 1973-1997. *J Neurosurg* 2003;99:458–66.
30. Grossman R, Mukherjee D, Chaichana KL, *et al*. Complications and death among elderly patients undergoing pituitary tumour surgery. *Clin Endocrinol* 2010;73:361–8.
31. Seicean A, Seicean S, Schiltz NK, *et al*. Short-term outcomes of craniotomy for malignant brain tumors in the elderly. *Cancer* 2013;119:1058–64.
32. Hulley Sb CS, Ws B, Grady D, *et al*. *Designing clinical research: an epidemiologic approach*. 4th ed. (M). City: Philadelphia: PA: Lippincott Williams & Wilkins, 2013:75. Appendix 6B.
33. Sleigh JW. Depth of anesthesia: perhaps the patient isn't a submarine. *Anesthesiology* 2011;115:1149–50.
34. Bennett C, Voss LJ, Barnard JP, *et al*. Practical use of the raw electroencephalogram waveform during general anesthesia: the art and science. *Anesth Analg* 2009;109:539–50.
35. Soehle M, Wolf CF, Priston MJ, *et al*. Propofol pharmacodynamics and bispectral index during key moments of awake craniotomy. *J Neurosurg Anesthesiol* 2016:1.
36. Conte V, L'Acqua C, Rotelli S, *et al*. Bispectral index during asleep-awake craniotomies. *J Neurosurg Anesthesiol* 2013;25:279–84.
37. Shiraishi T, Uchino H, Sagara T, *et al*. A comparison of frontal and occipital bispectral index values obtained during neurosurgical procedures. *Anesth Analg* 2004;98:1773–5. table of contents.
38. Messina AG, Wang M, Ward MJ, *et al*. Anaesthetic interventions for prevention of awareness during surgery. *Cochrane Database Syst Rev* 2016;10:Cd007272.
39. Law CJ, Jacobson GM, Kluger M, *et al*. Randomized controlled trial of the effect of depth of anaesthesia on postoperative pain. *Br J Anaesth* 2014;112:675–80.
40. Sahni N, Anand LK, Gombar K, *et al*. Effect of intraoperative depth of anesthesia on postoperative pain and analgesic requirement: a randomized prospective observer blinded study. *J Anaesthesiol Clin Pharmacol* 2011;27:500–5.
41. Farag E, Chelune GJ, Schubert A, *et al*. Is depth of anesthesia, as assessed by the Bispectral Index, related to postoperative cognitive dysfunction and recovery? *Anesth Analg* 2006;103:633–40.
42. An J, Fang Q, Huang C, *et al*. Deeper total intravenous anesthesia reduced the incidence of early postoperative cognitive dysfunction after microvascular decompression for facial spasm. *J Neurosurg Anesthesiol* 2011;23:12–17.