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Dexmedetomidine *vs* propofol-remifentanil conscious sedation for awake craniotomy: a prospective randomized controlled trial†‡

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Abstract

Background: Awake craniotomy (AC) is performed for the resection of brain tumours in close proximity to areas of eloquent brain function to maximize reduction of tumour mass and minimize neurological injury. This study compares the efficacy and safety of dexmedetomidine vs propofol-remifentanil-based conscious sedation, during AC for supratentorial tumour resection.
Methods: Prospective, randomized, controlled trial including 50 adult patients undergoing AC who were randomly assigned to a dexmedetomidine (DEX group, *n*=25) or propofol-remifentanil group (P-R group, *n*=25). The primary outcome was the ability to perform intraoperative brain mapping assessed on a numeric rating scale (NRS). Secondary outcome was the efficacy of sedation measured by the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale. Other outcome measures including haemodynamic and respiratory variables, pain, sedation and anxiety scores, adverse events, and patient satisfaction were also compared.
Results: There were no differences between DEX and P-R groups regarding the ability to perform intraoperative brain mapping [mean NRS score (95% CI): 10.0 (9.9–10.0) *vs* 9.7 (9.5–10.0), *P*=0.13] and level of sedation during mapping [mean OAA/S score (95% CI): 4.1 (3.5–4.7) *vs* 4.3 (3.9–4.7), *P*=0.51], respectively. Respiratory adverse events were more frequent in the P-R group (20 *vs* 0%, *P*=0.021). Heart rate was significantly lower in the DEX group across time (*P*<0.001); however, the need for treatment of bradycardia was not different between groups.
Conclusions: Quality of intraoperative brain mapping and efficacy of sedation with dexmedetomidine were similar to propofol-remifentanil during AC for supratentorial tumour resection. Dexmedetomidine was associated with fewer respiratory adverse events.
Clinical trial registration: NCT01545297.

Key words: anaesthetics, intravenous; conscious sedation; craniotomy; dexmedetomidine; propofol; remifentanil

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Editor's key points

- For brain tumours in close proximity to eloquent areas, intraoperative mapping can help optimize outcomes.
- To facilitate this, an 'awake craniotomy' technique is performed to facilitate wakefulness during mapping.
- The optimal sedation or anaesthetic technique for awake craniotomy has not been identified.
- In this randomized controlled trial the authors compared dexmedetomidine and propofol-remifentanil techniques.

Awake craniotomy (AC) is an accepted procedure for resection of a brain tumour, located in close proximity to areas of eloquent brain function, to achieve maximal surgical reduction of tumour mass without injuring important functional areas of the brain, such as the motor, language, or sensory cortex.[1–4] A variety of anaesthetic techniques have been used for AC, ranging from an 'asleep-awake-asleep' technique, with or without mechanical ventilation, to the management of 'fully awake' patients with local or regional anaesthesia of the scalp.[5 6] The required level of sedation and analgesia varies throughout the different stages of surgery, but most importantly, the patient needs to be awake and alert during brain mapping.[7] Different i.v. sedative drugs have been used in AC; for conscious sedation or monitored anaesthesia care, many anaesthetists choose a combination of propofol and an ultra-short-acting opioid such as remifentanil.[8–11] However, in AC patients with an unsecured airway, the use of propofol sedation in combination with opioids has been associated with intraoperative airway and/or respiratory complications, and poor patient cooperation during cortical mapping.[9 12–14]

Dexmedetomidine is a potent, highly selective α_2-adrenoceptor agonist[15–17] with sedative, anxiolytic, analgesic, opioid-sparing,[18] and sympatholytic effects.[16] In contrast to other sedative agents, dexmedetomidine is not associated with respiratory depression.[16 19] As a result of predictable pharmacokinetics and a rapid distribution half-life of 5–6 min[15 17] after bolus injection, dexmedetomidine may be titrated to a desired effect. Prolonged infusions of dexmedetomidine, however, may lead to delayed sedative effects after discontinuation of the drug because of a longer context-sensitive half-life.[20–23] The hypnotic properties of dexmedetomidine are mediated via hyperpolarization of noradrenergic neurons in the *locus ceruleus*. Fundamental research suggests that dexmedetomidine converges on a natural sleep pathway to exert its sedative effect.[24] This unique state of sedation, also called 'collaborative sedation',[25] may be useful for AC, which requires a deep level of sedation during painful and stimulating operative procedures on the one hand, and sufficient patient cooperation during mapping of eloquent function on the other.

The purpose of this study was to compare the use of dexmedetomidine *vs* propofol-remifentanil-based conscious sedation, in patients undergoing AC for the resection of supratentorial brain tumours. We hypothesized that there would be no difference in the ability to perform intraoperative brain mapping between dexmedetomidine and propofol-remifentanil, and that both sedation techniques would have comparable efficacy and safety profiles.

Methods

Trial design

The University Health Network Research Ethics Board provided ethical approval for this study (Ethical Committee No. 11-0607-A). All study participants provided written informed consent. We conducted a prospective, double-blind, randomized trial. It was conducted according to the revised Declaration of Helsinki of the World Medical Association and ICH GCP guidelines for good clinical trial practice. The study was registered on ClinicalTrials.gov (NCT01545297) before patient enrolment.

Participants and study setting

Study participants were recruited at the Toronto Western Hospital, University Health Network, Toronto, Canada. We included patients aged ≥18 yr, ASA physical status I–III, undergoing elective AC for the resection of a supratentorial brain tumour, using a conscious sedation technique. Exclusion criteria were severe cardiovascular or respiratory disease (ASA grade ≥IV), pregnancy, allergies to the drugs being used, known alcohol or substance abuse, and expected communication difficulties with the patient.

Interventions

Before surgery, 50 eligible patients were equally randomized to receive either dexmedetomidine (DEX group) or propofol-remifentanil (P-R group) infusions. The loading dose of dexmedetomidine was 1 μg kg^{-1} over 10 min, followed by a maintenance infusion titrated to effect (doses ranging from 0.2–1 μg kg^{-1} h^{-1}). Continuous infusion rates of propofol and remifentanil were 25–150 and 0.01–0.1 μg kg^{-1} min^{-1}, respectively. Dosing of all study drugs for surgical stages other than brain mapping was adjusted to achieve a targeted level of sedation of 2–4 points, on the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale.[26]

Anaesthetic management

Intraoperative anaesthetic management was standardized by using the predefined sedation protocols in both groups. No premedication was used. The patient was comfortably positioned (supine or lateral) on the operating table. Vital signs were recorded using ASA standard monitors: non-invasive bp monitoring, ECG, and pulse oximetry (SpO_2). Arterial lines or urinary catheters were not inserted routinely. All patients were breathing spontaneously and received supplemental oxygen at 4 l min^{-1} (inducing a mean inspired fraction of oxygen of approximately 36%) via nasal prongs. Naso- or oropharyngeal airway devices were not used. The presence of end-tidal carbon dioxide ($EtCO_2$) was monitored at the oxygen delivery nasal prongs port to determine respiratory rate (RR).

After establishment of peripheral venous access in the operating room, each patient received fentanyl 50 μg i.v., and then the study drug infusions were started according to the respective sedation protocol. Approximately 10 min later, the sites of pin insertion for rigid head fixation (Sugita frame) were infiltrated with local anaesthetic agent (2% lidocaine with 1:200,000 epinephrine) by the neurosurgeon. Infiltration of the scalp was performed using 0.25% bupivacaine with 1:200,000 epinephrine to produce a 'ring block' around the incision. The overall management of the anaesthetic with respect to adjustments of the drug infusions and the administration of all other required medications was left up to the attending anaesthetist. At any time during the procedure, when excessive pain was expected, or if the patient complained of pain or discomfort, the infusion rates of dexmedetomidine (DEX group) or remifentanil (P-R group) were increased. If necessary, additional fentanyl 25–50 μg i.v. was administered. If sedation was inadequate in either group, the infusion rates were increased at first. Rescue medication consisting of a propofol bolus (20–30 mg i.v.) was given when first-line treatment

failed. Ten min before brain mapping, propofol was discontinued, and dexmedetomidine and remifentanil infusions were reduced. Minimal infusion rates of dexmedetomidine (0.1–0.4 μg kg^{-1} h^{-1}) in the DEX group, and remifentanil (0.01–0.05 μg kg^{-1} min^{-1}) in the P-R group were continued during mapping. Mapping for motor, sensory and/or speech functions was performed after placement of a stimulating electrode on the cortical surface by the neurosurgeon.[2] The anaesthetist observed for any movements of the face, arm or leg. Motor strength was tested by asking the patient to move their hand (fingers) or foot (dorsiflexion) against resistance. Patients were advised to note any changes in sensation. Language was tested by asking the patient to count or name lists of objects while observing for speech arrest or hesitation. The duration of brain mapping was approximately 10 min. Subsequently, study drug infusions were resumed for tumour resection and closure of the craniotomy. Patients received fentanyl 0.5–1 μg kg^{-1} i.v. if they complained of headache or other pain at the end of the procedure.

After surgery, patients were monitored in the postanaesthetic care unit (PACU) for 2 h before being discharged to the ward or day surgery unit. In the PACU, all standard monitoring of a neurological patient was performed, and postoperative pain was treated according to a standard protocol with a combination of oral acetaminophen and morphine or fentanyl i.v. or oral oxycodone. Ondansetron 4 mg, and/or dimenhydrinate 50 mg, and/or metoclopramide 20 mg and/or dexamethasone 4 mg i.v. were administered for postoperative nausea and vomiting when needed. After discharge from the PACU, the care of the patient including the administration of analgesics and discharge from the hospital was determined by the surgical team.

Outcome variables

The primary outcome measure was the quality of intraoperative brain mapping. The ability of the patient to cooperate and perform cortical mapping was assessed on a 10-point numerical rating scale (NRS; 0=unsatisfactory; 10=excellent). Mapping was considered successful when the NRS score was ≥8. The level of sedation was recorded at the time of mapping and throughout the procedure using the modified OAA/S scale. Using visual analogue scales (VAS), patients were asked to evaluate levels of pain (0=no; 1–3=mild; 4–6=moderate; 7–10=severe pain) and anxiety (0–1=no or mild; 2–3=moderate; 4–5=severe anxiety). This assessment was repeated at 12 successive time points throughout the procedure (T0, baseline; T1, headpin insertion; T2, 5 min after T1; T3, local anaesthetic infiltration to incision; T4, skin incision; T5, craniotomy (bone work); T6, dura opening; T7, brain mapping; T8, start of tumour resection; T9, 30 min after T8; T10, skin closure; T11, admission to PACU; and T12, 120 min after T11).

Secondary outcome measures included the incidence of adverse events such as respiratory depression or airway obstruction, haemodynamic instability, failure to provide adequate analgesia, and all intra- and immediate postoperative complications. Heart rate (HR), mean arterial pressure (MAP), $S_{p_{O_2}}$, and RR were recorded at the 12 successive time points (T0–T12). Haemodynamic instability (arterial hypertension or hypotension, cardiac arrhythmia) and respiratory events (airway obstruction, apnoea/hypoventilation, oxygen desaturation), were defined as an adverse event when a treatment intervention (administration of a pharmacological agent for haemodynamic events, airway manoeuvres and/or diminution of study drug infusion for respiratory events) was required.

Preoperative variables included basic patient characteristics, clinical characteristics and medical co-morbidities. Assessment of the condition of the brain (lax or tight) upon opening of the dura mater and any intraoperative neurological complication (e.g., seizures, or new onset neurological deficits) were noted. Other intraoperative patient complaints or events (e.g., cold/shivering, nausea and vomiting, restlessness, fatigue, and need for conversion to general anaesthesia) were also recorded. In the PACU, the amount of opioid and antiemetic administered and the incidence of adverse events were noted. Testing of memory and cognitive function was also performed using the Short Portable Mental Status Questionnaire (SPMSQ[27]; Supplementary data, Table S1) at 2 and 24 h after surgery. At 24 h after surgery, the patients were interviewed in person and asked regarding any adverse events such as excessive pain, nausea and vomiting. They were asked how satisfactory were their intraoperative pain management and overall level of comfort, recall of the intraoperative experience including pain, anxiety and discomfort, and their willingness to repeat surgery, if needed, using the same anaesthetic technique. If the patient had been discharged home the day of surgery, a telephone interview was conducted. Length of hospital stay and final postoperative destination of patients (in- or outpatient surgery, need for unplanned postoperative hospital admission) were noted.

Sample size

A change of 25% in the ability to perform satisfactory intraoperative brain mapping was considered to be of clinical importance. To detect a mean difference of 2.5 points on the 10-point NRS for mapping quality between the DEX and P-R groups, a sample size of 25 subjects per group was required (total of 50 subjects), considering a 2-sided test with α=0.05, power of 90%, standard deviation of 1, and assuming a 10% drop-out rate.

Randomization

We performed simple randomization of participants to the DEX and P-R groups. One investigator generated the random allocation sequence and provided allocation concealment by using sequentially numbered, sealed, opaque envelopes. A second investigator implemented the randomization method and enrolled participants.

Blinding

A blinded investigator that was not directly involved in the anaesthetic management of the patients, collected all intra- and postoperative data. Patient and neurosurgeon were blinded to group allocation; however, it was not practical to blind the attending anaesthetist to preoperative and intraoperative data, as this information was essential for the medical care of patients. For blinding purposes, two drug infusion pumps were used in every patient. Study drug infusion pumps and i.v. connection lines were concealed to avoid identification.

Statistical analysis

Analysis was performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC, USA). All analyses were undertaken on a modified intention-to-treat set, comprising all patients who had a baseline value during the intraoperative assessment. Continuous variables and univariate differences between DEX and P-R groups were compared using the Wilcoxon rank-sum test, categorical variables using the χ^2 test. Data are expressed as mean (SD), or as median [25–75% interquartile range (IQR)] for continuous variables, and count (%) for categorical variables.

Differences in sedation, pain, and anxiety scores between the groups were compared using a one-way analysis of variance (ANOVA). Repeated-measures ANOVA were conducted to assess variations in MAP, HR, RR, and $S_{p_{O_2}}$ over time. For each of the responses, the interaction between anaesthetic technique and time was first tested and kept in the model if it reached statistical significance, or was removed otherwise. An unstructured variance-covariance structure was used for the within-subject factor. Least-squares means differences between the groups were compared; associated 95% confidence intervals (CI) and *P* values are presented. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

One-hundred and four patients were screened for study eligibility between October 2012 and December 2014 (Fig. 1). Fifty-four patients were excluded before randomization. The remaining 50 patients were equally randomized to the DEX group ($n=25$) or the P-R group ($n=25$). No participant was lost to follow-up; however, two patients in the DEX group were excluded from the analysis because of incorrect allocation in one, and conversion to a general anaesthetic by surgeon's request at the start of the procedure in another.

Baseline patient characteristics and clinical characteristics are shown in Table 1. There were no differences in patient age, weight, height, gender, preoperative ASA physical status and medical co-morbidities, and anaesthesia duration between DEX and P-R groups. Histological diagnosis of the lesions resected included glioma (DEX group, $n=12$; P-R group, $n=11$), metastatic (DEX group, $n=6$; P-R group, $n=10$), and other (DEX group, $n=5$; P-R group, $n=4$) (all $P>0.05$). Arterial lines were inserted for clinical purposes in four patients (DEX group, $n=2$; P-R group, $n=2$). Intraoperatively, patients received total doses [mean (SD)] of fentanyl [DEX group, 119 (53) μg; P-R group, 89 (39) μg], propofol [DEX group, 160 (110) mg; P-R group, 596 (531) mg], dexmedetomidine [DEX group, 141 (36) mg], and remifentanil [P-R group, 310 (360) μg].

Outcome variables

Intraoperative brain mapping was successful in all patients [overall mean NRS score (SD): 9.84 (0.48), range 8–10]. There was no difference between DEX and P-R groups in terms of the ability to perform brain mapping [mean NRS score (95% CI): DEX group, 10.0 (9.9–10.0) *vs* P-R group, 9.7 (9.5–10.0), $P=0.13$].

No difference between groups was found regarding the level of sedation at the time of mapping [mean OAA/S score (95% CI): DEX group, 4.1 (3.5–4.7) *vs* P-R group, 4.3 (3.9–4.7), $P=0.51$]. The OAA/S scores were significantly lower in the DEX group at

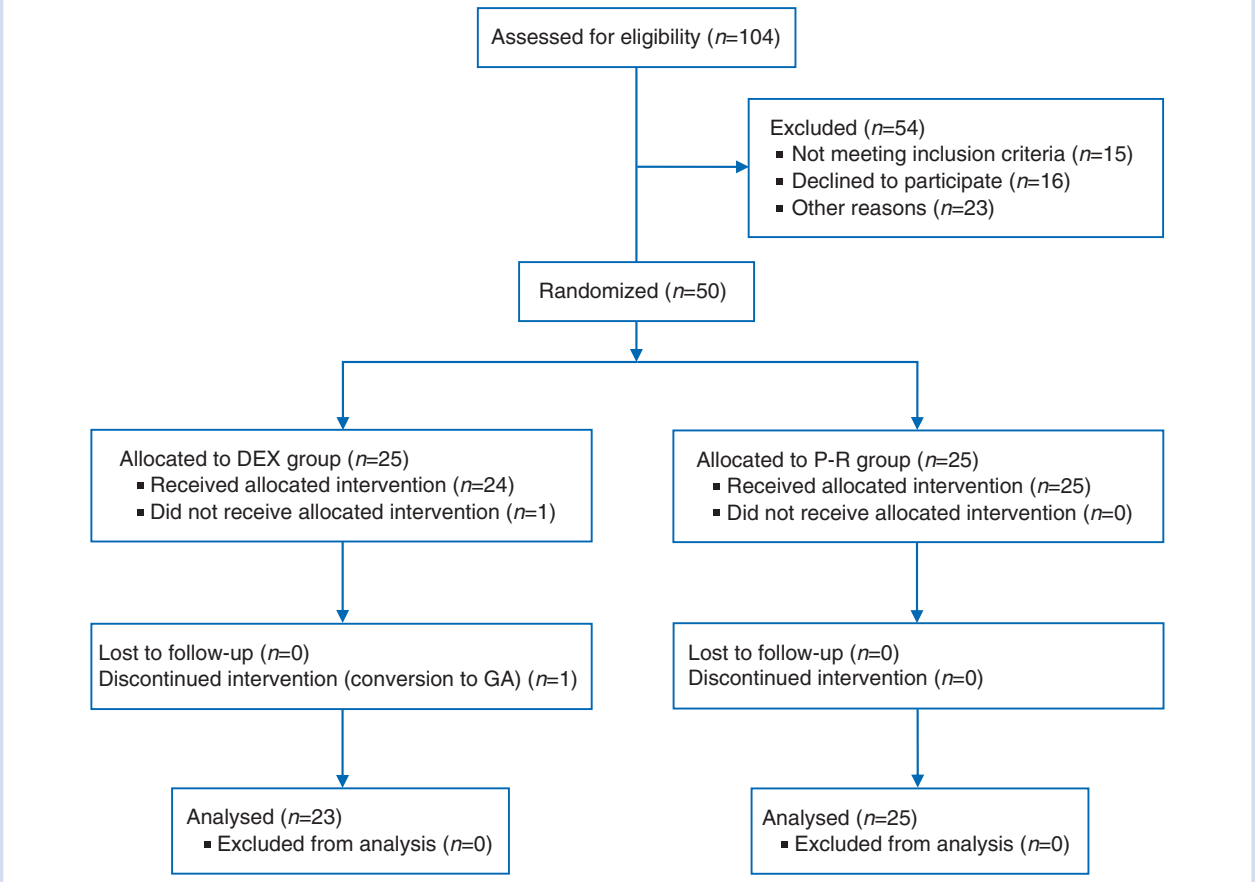

Fig 1 CONSORT flow diagram. Fifty subjects were randomized; one subject (DEX group) was eliminated because of incorrect allocation, and one subject (DEX group) was eliminated because of unexpected intraoperative conversion to a general anaesthetic. DEX group, dexmedetomidine group; GA, general anaesthetic; P-R group, propofol-remifentanil group.

Table 1 Baseline patient characteristics and clinical characteristics. Data are expressed as mean (SD) or count (%), except for age [mean (range)] and procedure duration [median (25–75% interquartile range)]. DEX group, dexmedetomidine group; IQR, interquartile range; P-R group, propofol-remifentanil group

	All patients (*n*=48)	P-R group (*n*=25)	DEX group (*n*=23)	*P* value
Baseline patient characteristics				
Age [mean (range); yr]	57.4 (27–88)	53.8 (27–80)	61.4 (36–88)	0.11
Weight [mean (SD); kg]	75.9 (15.2)	73.6 (12.3)	78.4 (17.7)	0.28
Height [mean (SD); cm]	168 (14)	169 (9)	166 (17)	0.98
BMI [mean (SD); kg m^{-2}]	27.4 (6.8)	25.7 (3.9)	29.3 (8.6)	0.07
Gender: male/female [*n* (%)]	30/18 (62.5/37.5)	16/9 (64/36)	14/9 (60.9/39.1)	0.82
ASA physical status: II/III [*n* (%)]	8/40 (16.7/83.3)	4/21 (16/84)	4/19 (17.4/82.6)	0.90
Medical co-morbidities [*n* (%)]				
Preoperative seizure	21 (44)	10 (40)	11 (48)	0.59
Respiratory	6 (13)	4 (16)	2 (9)	0.44
Obstructive sleep apnoea	4 (8)	1 (4)	3 (13)	0.26
Cardiac	7 (15)	4 (16)	3 (13)	0.77
Diabetes	3 (6)	1 (4)	2 (9)	0.50
Procedure duration [median (IQR); min]	121 (109–142)	125 (108–177)	115 (108–137)	0.44

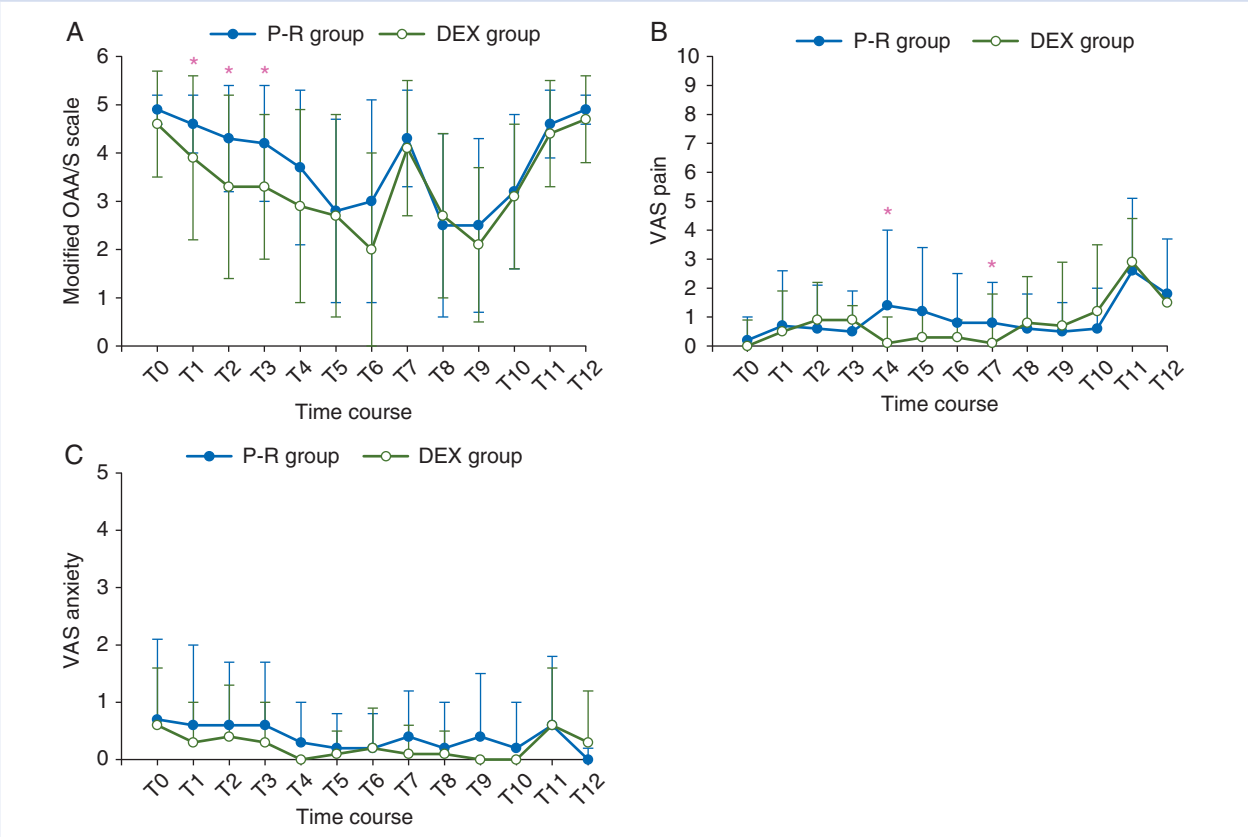

Fig 2 (A) Modified Observer's Assessment of Alertness/Sedation (OAA/S) scale (numeric value), (B) visual analogue scale for pain (VAS pain, numeric value), and (C) visual analogue scale for anxiety (VAS anxiety, numeric value) were assessed at consecutive time points (T0–T12). Study drug infusions were started at T0 and ended at T10. Results are shown as means (SD). DEX group, dexmedetomidine group; P-R group, propofol-remifentanil group; T0, intraoperative baseline; T1, headpin insertion; T2, 5 min after T1; T3, local anaesthetic infiltration to incision; T4, skin incision; T5, craniotomy (bone work); T6, dura opening; T7, brain mapping; T8, start of tumour resection; T9, 30 min after T8; T10, skin closure; T11, admission to PACU; T12, 120 min after T11. *$P<0.05$.

intraoperative time points T1–T3 [headpin insertion (P=0.040), 5 min after headpin insertion (P=0.041), and local anaesthetic infiltration to incision (P=0.018)] (Fig. 2). Arousal times after discontinuation of study drug infusion for cortical mapping were comparable between groups (approximately 5–8 min). VAS for pain was significantly lower in the DEX group at T4 [skin incision (P=0.026)] and T7 [brain mapping (P=0.031)]. VAS for anxiety was not different between groups throughout the procedure.

Figure 3 shows the time course of haemodynamic and respiratory outcome variables. MAP was significantly lower in the DEX

group at intraoperative time points T6–T8 [dura opening (P=0.026); brain mapping (P=0.007); start of tumour resection (P=0.022)] and T11–T12 [admission to PACU (P<0.001); 120 min after admission to PACU (P=0.004)]. An interaction effect of treatment group and time was detected for MAP (P=0.044). Repeated-measures ANOVA showed a significantly lower HR [mean difference (95% CI): −13.8 (−19.3, −8.4) beats min^{-1}, P<0.001] over time in the DEX group. RR was significantly lower in the P-R group at time points T8 [start of tumour resection (P=0.030)] and T10 [skin closure (P=0.002)]. There was no difference SpO_2 between groups throughout the procedure.

Table 2 shows the distribution of intraoperative adverse events. The total incidence of respiratory adverse events with need for intervention was lower in the DEX group compared with the P-R group (0 *vs* 20% respectively, P=0.021). These events were all short periods of airway obstruction and apnoea, and all occurred during or immediately after the insertion of head pins, before draping of the surgical site. Airway obstruction and apnoea were quickly treated with jaw thrust and/or brief mask ventilation; the insertion of a naso- or oropharyngeal airway device was not required at any time. Respiratory adverse events did not occur in either group during the remaining surgical time. There was no difference between groups regarding the incidence of haemodynamic instability, occurrence of a tight brain, new onset neurological deficits, seizures, excessive pain, psychomotor agitation, or nausea and vomiting. Cardiovascular adverse events, as defined per study protocol, consisted of arterial hypotension treated with ephedrine (n=2) and phenylephrine (n=1), and arterial hypertension treated with labetalol (n=1) and hydralazine (n=2). One patient (P-R group) developed supraventricular tachycardia at the end of tumour resection and was treated with labetalol and esmolol, but required cardioversion in the PACU.

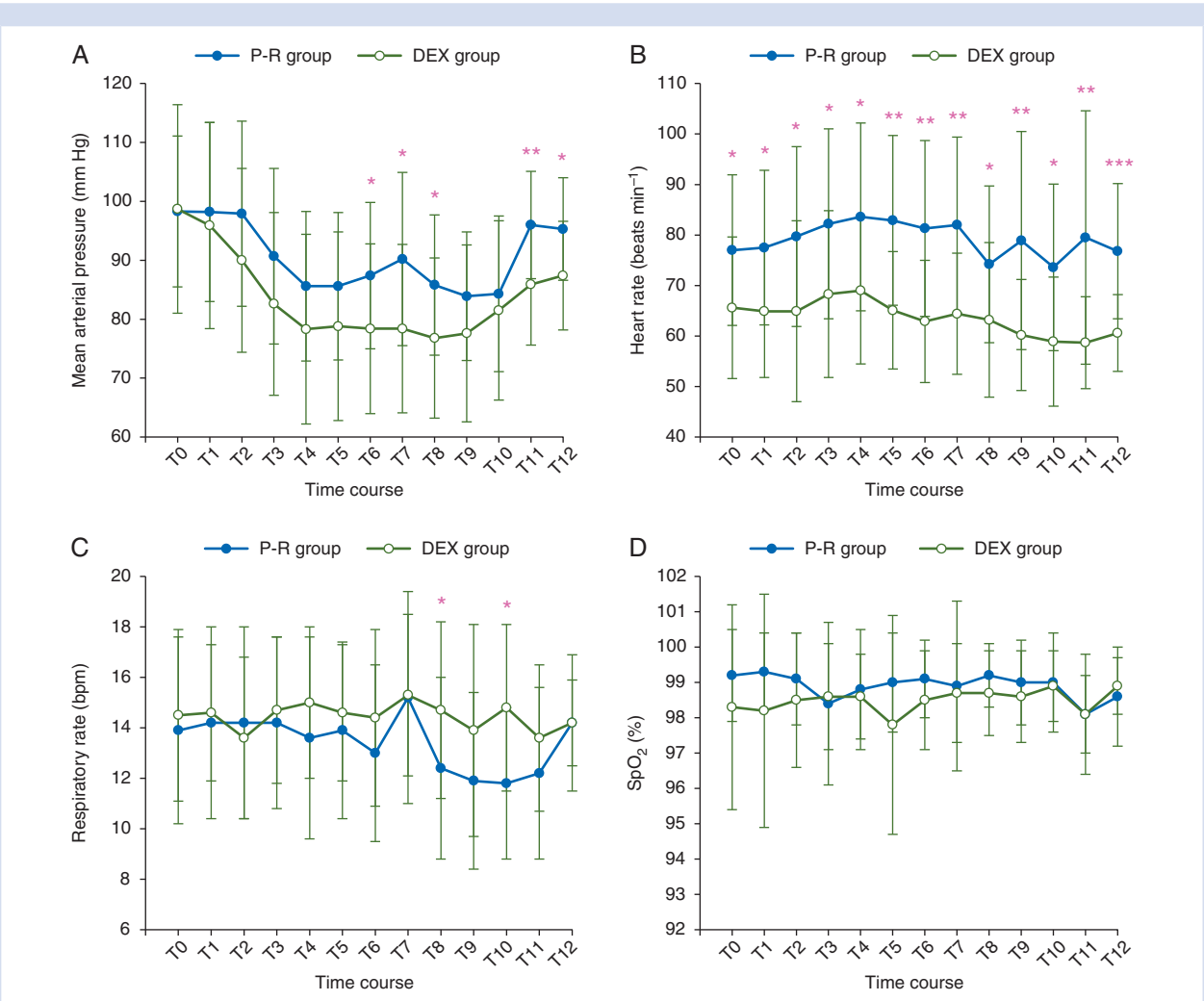

Fig 3 (A) Mean arterial pressure (MAP, mm Hg), (B) heart rate (HR, beats min^{-1}), (C) respiratory rate (RR, bpm), and (D) peripheral oxygen saturation ($S_{p_{O_2}}$, %) were assessed at consecutive time points (T0–T12). Study drug infusions were started at T0 and ended at T10. Repeated-measures ANOVA showed a significantly lower HR [mean difference (95% CI): −13.8 (−19.3, −8.4) beats min^{-1}, P<0.001] over time in the DEX group. Ranges of recorded values for MAP, HR, RR and $S_{p_{O_2}}$ in the DEX group were 50–135 mm Hg, 39–110 beats min^{-1}, 5–25 bpm and 86–100%, respectively; ranges for MAP, HR, RR and $S_{p_{O_2}}$ in the P-R group were 49–136 mm Hg, 46–150 beats min^{-1}, 6–26 bpm and 90–100%, respectively. Results are shown as means (SD). DEX group, dexmedetomidine group; P-R group, propofol-remifentanil group; T0, intraoperative baseline; T1, headpin insertion; T2, 5 min after T1; T3, local anaesthetic infiltration to incision; T4, skin incision; T5, craniotomy (bone work); T6, dura opening; T7, brain mapping; T8, start of tumour resection; T9, 30 min after T8; T10, skin closure; T11, admission to PACU; T12, 120 min after T11. *P<0.05; **P<0.001; ***P<0.0001.

Table 2 Incidence of intraoperative adverse events. Data are expressed as count (%). CI, confidence interval; DEX group, dexmedetomidine group; P-R group, propofol-remifentanil group; RR, relative risk

	P-R group (*n*=25)	DEX group (*n*=23)	RR	95% CI	*P* value
Respiratory, all events combined [*n* (%)]	5 (20)	0	10.15	0.59–174.04	0.023
Cardiovascular, all events combined [*n* (%)]	4 (16)	4 (17)	0.92	0.26–3.26	0.90
Arterial hypertension	2 (8)	1 (4)	1.84	0.18–18.96	0.60
Arterial hypotension	1 (4)	2 (9)	0.46	0.04–4.74	0.50
Cardiac arrhythmia	1 (4)	1 (4)	0.92	0.06–13.87	0.95
Neurological [*n* (%)]					
Tight brain	2 (8)	0	4.62	0.23–91.35	0.17
New neurological deficit	2 (8)	0	4.62	0.23–91.35	0.17
Seizure	0	3 (12)	0.13	0.01–2.42	0.06
Other [*n* (%)]					
Excessive pain	5 (20)	5 (22)	0.92	0.31–2.77	0.88
Psychomotor agitation	4 (16)	1 (4)	3.68	0.44–30.56	0.19
Vomiting	1 (4)	0	2.80	0.12–64.77	0.33
Patients with ≥1 adverse event [*n* (%)]	13 (52)	12 (52)	0.99	0.58–1.72	0.99

One patient (DEX group) experienced a short episode of bradycardia and hypotension (exact values for HR and MAP missing) at the end of the procedure and was treated with atropine. Four patients in the P-R group developed intraoperative psychomotor agitation with disinhibition (*n*=1), or with emotional upset (*n*=3), of which one was treated with midazolam. One patient in the DEX group complained of being 'too awake'. Seizures occurred in the DEX group during brain mapping (*n*=2) and tumour resection (*n*=1), and were successfully treated with both cold saline solution administered to the brain's surface and propofol bolus.

Postoperatively, there was no difference in the incidence of other complications. One patient in the P-R group had a seizure. The total dose of analgesia administered in the PACU was calculated by converting the fentanyl, morphine, codeine, and oxycodone doses to morphine equivalents. In the DEX group, 15 patients (65%) required postoperative analgesia with a mean (SD) dose of morphine equivalents of 5.6 (3.3) mg; in the P-R group, 18 patients (72%) with a mean (SD) dose of 7.4 (3.8) mg (*P*=0.17). Antiemetic medication for prophylactic and/or therapeutic purposes was administered in three patients (13%) in the DEX group and 12 patients (48%) in the P-R group.

The cognitive performance measured at 2 h [mean SPMSQ score (SD): DEX group, 0.9 (1.4) *vs* P-R group, 1.3 (1.8), *P*=0.43] and at 24 h [DEX group, 1.5 (1.6) *vs* P-R group, 1.5 (1.4), *P*=0.96] was not different between the two groups, alike the degree of patient satisfaction and the level of recall of the procedure (Fig. 4). The final postoperative destination of patients included in the study did not differ between groups. Thirty-one participants (65%) were scheduled as outpatients and 14 (29%) as inpatients. Three patients (6%) that were initially planned for day surgery were admitted to the hospital after surgery as a result of a new neurological deficit (DEX group: *n*=1; P-R group: *n*=1) and mild confusion (DEX group: *n*=1).

Discussion

Dexmedetomidine and propofol-remifentanil-based conscious sedation, without airway manipulation, during AC for supratentorial tumour resection showed similar quality of intraoperative brain mapping and efficacy of sedation in this prospective, randomized, double-blind, comparative study. The incidence of intra- and postoperative cardiovascular, neurological, or other adverse events did not differ between the groups. However, the incidence of respiratory adverse events was significantly greater in the P-R group. The levels of perioperative pain and anxiety, patient satisfaction, and recall were all comparable. Compared with propofol-remifentanil, dexmedetomidine administration was associated with a decrease in HR throughout the procedure and a decrease in MAP during least stimulating surgical time points. However, the decrease in HR was not greater than 20% from baseline.

The anaesthetic management of an AC using a conscious sedation technique usually involves a combination of local anaesthesia to the scalp and i.v. agents to provide sedation, analgesia, and anxiolysis. Our institutional practice in patients undergoing AC for tumour surgery is to perform a 'ring block' infiltration of the incision site with bupivacaine, and to provide concomitant conscious sedation. An alternative to the 'ring block' technique is the selective regional anaesthesia to the nerves that innervate the scalp ('scalp block'),[28] using different local anaesthetic agents such as ropivacaine or levobupivacaine.[29] Local anaesthetic toxicity is rarely seen in AC.[28] Other anaesthetic techniques such as the 'asleep-awake-asleep' or the 'asleep-awake' technique, typically involving general anaesthesia and airway management (tracheal intubation or insertion of a laryngeal mask airway), have been successfully used for AC. However, when the conscious sedation technique is used, there is usually no or only minimal manipulation of the airway. Propofol sedation, commonly in combination with a short-acting opioid, is an effective technique for conscious sedation for AC,[9 14] achieving a high degree of patient satisfaction and acceptance.[10] Other groups recommend the use of target-controlled infusion (TCI),[30 31] unavailable at our institution, to guide the administration of i.v. anaesthetics to anticipate the transitions from general anaesthesia to the awake state during an AC. The use of TCI modes may also be helpful to prevent respiratory adverse effects arising from the pharmacological interaction of propofol and opioid. However, independently of the choice of anaesthetic technique, AC remains a challenging procedure. The key assets of an 'ideal' drug for conscious sedation are a large therapeutic index and predictable pharmacodynamics to ensure an adequate level of sedation and analgesia facing the rapid changes of surgical stimulation, yet permitting the collaboration of the awake patient in complex intraoperative brain mapping.

Dexmedetomidine produces a cooperative form of sedation, in which patients easily transition from sleep to wakefulness and task performance when aroused, and back to sleep when

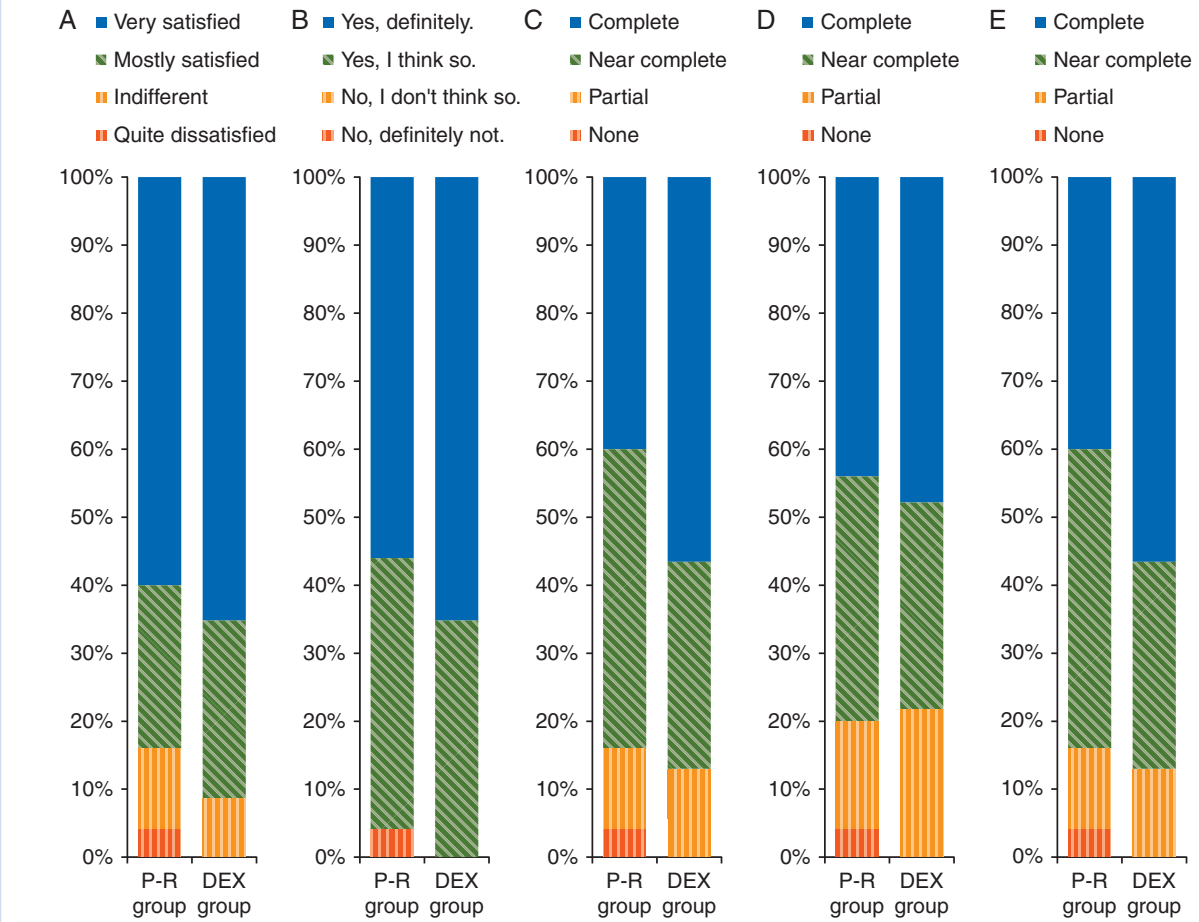

Fig 4 Patient satisfaction and recall of the surgical procedure (awake craniotomy) were assessed at 24 h using Likert scales. In a structured interview, patients were asked to rate their intraoperative experience by answering to the five following questions: (A) How satisfied were you with your pain management and overall level of comfort? (B) If you were to have surgery again, would you opt for the same method of management? (C) Recall of the intraoperative experience. (D) Recall of the level of intraoperative pain. (E) Recall of the level of intraoperative discomfort and anxiety. DEX group, dexmedetomidine group; P-R group, propofol-remifentanil group.

not stimulated.[32] Bekker and colleagues[33] first reported the use of dexmedetomidine in AC in 2001. Subsequent studies evaluating the influence of dexmedetomidine on the ability to perform intraoperative neurologic testing showed inconsistent results.[34–36] One recent case report[37] and several case series of awake craniotomies for tumour resection advocate an anaesthetic approach based on scalp nerve blocks and dexmedetomidine with[38] or without airway manipulation.[39 40] Another study compared the combinations of dexmedetomidine and remifentanil to propofol and remifentanil during AC using an 'asleep-awake-asleep' technique involving general anaesthesia with orotracheal intubation.[41] They found both to be effective and safe; however, there was a shorter arousal time from the sleep state for mapping with dexmedetomidine. The short arousal times in our study were likely as a result of relatively low levels of sedation before brain mapping and the relatively short overall duration of surgery.

The use of a sole anaesthetic agent may not be sufficient for all stages of an AC with a conscious sedation technique. The initial part of the procedure can be very stimulating and painful with the injection of local anaesthesia, followed by the insertion of the head pins. During this time the patient may require additional sedation and analgesia. It is important that the patient does not experience pain during this part of the procedure. Therefore, we administered an initial dose of fentanyl to all patients in our protocol. Also, our past experience had been that patients were frequently 'too awake' during periods of dexmedetomidine sedation alone, hence, we allowed the addition of rescue medication (propofol bolus), as needed. The opioid-sparing effects of dexmedetomidine used as an adjunct to anaesthesia during the perioperative period are well-documented.[18] But when used as a sole anaesthetic agent, dexmedetomidine may not offer the desired analgesic effects for all stages of AC, and thus, may not completely replace opioids.[42 43] A low-dose remifentanil infusion used along with dexmedetomidine may potentially help to achieve successful pain control.

The main safety concerns with conscious sedation in non-intubated patients are airway compromise, hypoventilation and oxygen desaturation. Most anaesthetic agents used during AC are associated with some respiratory depression.[12 14] While respiratory adverse events rarely occur when using a technique that involves intermittent general anaesthesia and invasive airway management,[44] spontaneously breathing patients undergoing AC may be at risk for airway obstruction or hypoventilation.[14]

In our study, we found an increased incidence of airway and/or respiratory adverse events within the P-R group. The patient's respiratory rate increased when propofol was stopped for brain mapping while it remained constant with dexmedetomidine.[45] In a systematic review of spontaneously breathing subjects receiving different sedative drugs for sleep endoscopy, all agents including dexmedetomidine caused some degrees of airway collapse.[46] Thus, dexmedetomidine alone may not cause a decrease in the respiratory rate or hypoventilation through a central effect on respiration, but one must be vigilant especially with the addition of other agents, such as opioids and/or propofol, as this may result in airway obstruction by relaxation of the pharyngeal muscles.[47] For this investigation, we did not measure $PaCO_2$ and used $EtCO_2$ merely for monitoring of RR in spontaneously breathing patients; however, prolonged alveolar hypoventilation associated with clinically important hypercapnia did not seem to occur in any of our patients.

A decrease in bp and heart rate is the most common cardiovascular effect of dexmedetomidine.[48–50] Clinically significant episodes of hypotension (45%) and bradycardia (14%) have been associated with dexmedetomidine infusion and may necessitate medical intervention in 10% and 3% of patients, respectively.[49] The relatively low incidence of haemodynamic adverse events during conscious sedation for AC found in both DEX and P-R groups is consistent with findings of previous studies.[41]

Intraoperative seizures have been reported to occur in up to 13% of patients undergoing AC for tumour resection.[51] The risk is particularly high during brain mapping when electrical current is directly applied to the motor cortex (20%).[52] Dexmedetomidine has been shown to decrease the seizure threshold in different animal models.[53 54] However, there are limited data on its effect on electroencephalographic responses in humans.[55 56] Several clinical investigations in patients diagnosed with epilepsy concluded that dexmedetomidine does not reduce seizure focus activity.[34 57 58] In our study, intraoperative seizures occurred only in the DEX group (n=3); however, in comparison to the P-R group, this finding did not reach statistical significance. Our sample size may have been too small to find any difference. While the anti-epileptic properties of propofol are known, further research should elucidate whether dexmedetomidine has a direct effect on the seizure threshold (by inhibition of central noradrenergic transmission), or if the absence of protective agents such as propofol renders patients more prone to seizures during AC.

Psychomotor agitation can be an important problem in patients undergoing complex neurosurgical procedures such as AC. Disinhibition and lack of cooperation have been described for low-dose propofol (1.3% of patients)[59] and benzodiazepine sedation, but do not seem to occur with dexmedetomidine.[32] Accordingly, we found a trend towards a higher incidence of intraoperative psychomotor agitation in the P-R group compared with the DEX group (P=0.19).

The overall management including the need for analgesia and incidence of adverse events in the PACU was not different between the two groups. We were unable to study the need and the amount of analgesia the patients required after discharge from PACU as the placement of patients varied. Overall, 58% of our patients went home on the same day as surgery, which is a common practice in our institution.[60 61] The SPMSQ was used as a simple test of memory and cognitive function, and there were no differences at either time of assessment. Previous studies have found high satisfaction in patients who underwent an AC; although recall of intraoperative events varied, most patients would have the similar technique of anaesthesia if required in the future.[10 60 62].

The current study has a number of limitations that should be considered. Although the patient, surgeon, and study investigator collecting intraoperative data were blinded to group allocation, it was not possible to blind the attending anaesthetist managing the patient for patient safety reasons. The behaviour of the anaesthetist might have influenced judgement of the surgeon and/or the study investigator, and this may be responsible for bias. The administration of anaesthetic agents being left to the discretion of the attending anaesthetist may have introduced additional bias. We acknowledge that our method of comparing the use of rescue medication in both groups may have been flawed, as some rescue drug administrations may have stayed undetected in the P-R group (e.g. when the attending anaesthetist temporarily increased infusion rates of propofol or remifentanil).

The overall duration of our procedures was relatively short [median time (IQR): 121 (109–142) min], and the brain mapping performed was not extensive in terms of examination technique and duration compared with other studies.[39 41] Thus, the conclusions from our study pertain only to AC for tumour, and may not be extrapolated to all other neurosurgical procedure performed as AC, demanding longer procedure times and more complex intraoperative neuropsychological testing.

Sample size was calculated only with respect to the primary outcome measure (NRS of the quality of intraoperative brain mapping); numerous other outcome variables reported in this study lack a specific power analysis. Likely, a larger sample size would be necessary to reveal potential differences between groups, e.g. in the incidence of adverse events.

We did not utilize a processed EEG-based monitor to evaluate depth of sedation. Some authors have advocated the use of bispectral index (BIS) monitoring to guide depth of anaesthesia during AC and to achieve predictable recovery from general anaesthesia, when applying an 'asleep-awake' protocol.[63] In this context, an association of TCI modes for drug administration and BIS may be helpful to reach fast transition times between anaesthetic states.[30 31] In our study, level of sedation was assessed using the OAA/S scale. Although this is a subjective scoring method based on clinical information, the OAA/S is a reliable and valid tool with a low inter-rater variability.[26] Previous investigations have also shown that the OAA/S scale correlates well with BIS during dexmedetomidine and propofol sedation.[64]

In conclusion, the ability to perform intraoperative brain mapping and the efficacy of dexmedetomidine was similar to propofol-remifentanil-based conscious sedation in AC, for supratentorial tumour resection. The use of dexmedetomidine and propofol-remifentanil during AC was safe. However, dexmedetomidine may offer distinct advantages in this indication because of a lower incidence of respiratory adverse events. Optimal dose regimen of sedatives and careful vigilance are the keys for successful conscious sedation during AC.

Ethics committee approval

Ethical approval for this study (ethical committee N° 11-0607-A) was provided by the University Health Network Research Ethics Board, 10th Floor, Room 1056, 700 University Ave, Toronto, ON, M5G 1Z5, Canada, Phone: +1 (416) 581-7849, on November 9, 2011.

Approval for this study (control N° 151753) was provided by Health Canada.

This report describes human research. This study was conducted with written informed consent from the study subjects and in respect of the revised Declaration of Helsinki.

The study was registered on ClinicalTrials.gov (NCT01545297) before patient enrolment.

This report describes a randomized controlled trial study. The author states that the report includes the items in the CONSORT checklist for randomized controlled trials.

This manuscript was screened for plagiarism with iThenticate.

Authors' contributions

Study design/planning: N.G., P.H.M.
Study conduct: N.G., S.B., L.V., J.M., P.H.M.
Data analysis: N.G.
Writing paper: N.G., P.H.M.
Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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