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Clinical Investigation

CLINICAL INVESTIGATION

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