Effect of Intraoperative Dexmedetomidine on Post-Craniotomy Pain

Ke Peng, MS; Xiao-hong Jin, MD; Si-lan Liu, MD; and Fu-hai Ji, MD

Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, China

ABSTRACT

Purpose: Pain management for patients who have undergone a craniotomy remains challenging. This study aimed to determine whether intraoperative dexmedetomidine could reduce postoperative pain, analgesic consumption, and possible adverse events in patients after craniotomy.

Methods: Eighty patients scheduled for elective supratentorial craniotomy under sevoflurane-fentanyl anesthesia were randomly allocated into two equal groups, to receive a continuous dexmedetomidine infusion of 0.5 μg/kg/h or placebo, beginning after induction and continuing until the start of skin closure. Intravenous tramadol (0.5 mg/kg) was administered to achieve an 11-point verbal rating scale (a discrete 0–10 scale) score of 4 or less in the postanesthesia care unit and, thereafter, on the ward. Pain scores, tramadol consumption, sedation scores, postoperative nausea and vomiting (PONV) scores, and other adverse events were recorded in the first 24 hours postoperatively.

Findings: Seventy-six patients were included in the analyses. Demographic data, surgical characteristics, and sedation levels were similar between the groups. Dexmedetomidine reduced pain scores (30 minutes, $P = 0.041$; 2 hours, $P = 0.021$) and tramadol consumption (0–2 hours, $P = 0.043$; 0–6 hours, $P = 0.006$; 0–12 hours, $P = 0.023$; 0–24 hours, $P = 0.040$) postoperatively. Dexmedetomidine also reduced PONV scores at 20, 60, 90, 120, and 240 minutes ($P = 0.038$, 0.022, 0.018, 0.037, 0.016, respectively). The dexmedetomidine group exhibited fewer PONV events that required treatment ($P = 0.005$).

Implications: Intraoperative dexmedetomidine infusion was effective for reducing pain and analgesic consumption after craniotomy. In addition, dexmedetomidine may help to reduce PONV in patients after craniotomy treated with tramadol postoperatively. Chinese Clinical Trial Register identifier: ChiCTR-TRC-13003598. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: analgesia, anesthesia, clinical trials, neurosurgery, pain management.

INTRODUCTION

Up to 80% of patients who undergo craniotomy experience acute postoperative pain that ranges from mild to severe, and up to 50% may continue to experience chronic headache for months after the operation.[1–5] However, this pain is often undertreated. Inadequate analgesia may lead to agitation, hypertension, and even postoperative intracranial hemorrhage. Opioids provide effective analgesia, but they may cause delayed awakening, hypercarbia, respiratory depression, increased intracranial pressure, and postoperative nausea and vomiting (PONV). Conservative analgesic regimes for neurosurgical procedures are common, and there is no consensus about postoperative pain management in this patient population.

Dexmedetomidine, a highly selective α-2 adrenoceptor agonist that provides sedative, anxiolytic, and analgesic effects without respiratory depression, is useful in neurosurgical procedures.[6] Recently, several studies found that the perioperative use of dexmedetomidine or clonidine can help to reduce opioid requirements and to potentiate analgesia in various surgical procedures (ie, abdominal, gynecologic, urologic, and spinal surgeries, and pediatric procedures).[7–9] According to our meta-analysis of dexmedetomidine as an anesthetic adjuvant for intracranial procedures, few studies have focused on the analgesic effect of dexmedetomidine infusion during intracranial surgery.[10] Therefore, this randomized double-blind placebo-controlled study aimed to determine whether

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intraoperative dexmedetomidine could reduce postoperative pain, analgesic consumption, and possible adverse events in patients who have undergone a craniotomy.

METHODS

Patients

This study was approved by the institutional review board for human subjects and was registered at www.chictr.org. All participants gave their written informed consent. Patients between the ages of 18 and 65 years with American Society of Anesthesiologists (ASA) classification I to II, undergoing elective supratentorial craniotomy for the resection of a brain tumor or intracranial vascular lesion, were eligible for inclusion in the study. Exclusion criteria were known allergy to the medications used in the study, ASA classification $\geq$ III, body mass index (BMI; calculated as weight divided by height squared; kg/m^2) >40 or <15, significant cardiopulmonary dysfunction, significant renal or liver disease, chronic pain, long-term opioid or benzodiazepine use, alcohol abuse, a preoperative Glasgow Coma Scale <15, intracranial hypertension, and uncontrolled epilepsy. Patients were informed preoperatively about the use of the verbal rating scale (VRS; a discrete 0–10 scale), where 0 represented no pain and 10 indicated the worst pain imaginable.

A computer-generated randomization table was used to assign the subjects to either the dexmedetomidine group or the placebo group. Randomization was performed by an independent anesthesia assistant. An anesthesiologist who was not involved in the study prepared study solutions that contained either dexmedetomidine or normal saline. The dexmedetomidine was diluted with saline to a final concentration of 4 μg/mL. All patients, anesthesiologists, surgeons, and postoperative observers were blinded to the group allocation.

Perioperative Management

On arrival at the operating room, a central venous catheter was inserted via the right subclavian vein, and an arterial line was inserted into the radial artery of the nondominant forearm under local anesthesia. Standard monitoring included pulse oximetry, electrocardiogram, arterial blood pressure, central venous pressure, and end-tidal carbon dioxide.

General anesthesia was induced with propofol (1.5–2 mg/kg) and fentanyl (3–4 μg/kg). Tracheal intubation was facilitated with cisatracurium (0.2 μg/kg). All patients received 0.1 mg/kg dexamethasone. After intubation, the lungs were ventilated at 8 mL/kg tidal volume with 0–5 mm Hg positive end-expiratory pressure (Drager Julian, Germany). The frequency was set to keep the end-tidal carbon dioxide within the range of 28 to 35 mm Hg. Anesthesia was maintained with 1% to 3% sevoflurane in 60% oxygen and 0.5-μg/kg increments of fentanyl. If sevoflurane and fentanyl were not sufficient to attenuate the hemodynamic responses, vasoactive drugs (nicardipine, nitroglycerin, and esmolol) were used. Ephedrine (5 mg) or phenylephrine (50 μg) was administered to treat hypotension (systolic arterial pressure <90 mm Hg or mean arterial pressure <65 mm Hg), and bradycardia (heart rate <40 beats/min) was treated with 0.5-mg boluses of atropine. Intravenous 1 g/kg mannitol infusions over 15 minutes and hyperventilation were used to treat excessive brain swelling.

A continuous infusion of 0.5 μg/kg/h dexmedetomidine (dexmedetomidine group) or placebo (control group) was started after induction and continued until the start of skin closure. There was no scalp infiltration with local anesthetics nor were other analgesics administered throughout the surgery. After surgery, all patients were extubated when they fulfilled the standard clinical criteria for oxygenation (pulse oximetry $>$ 95% during spontaneous ventilation, respiratory rate $<$ 35 breaths/min, adequate respiratory drive and muscle strength), hemodynamics (hemodynamic stability, defined as variability within $\pm$20%), and airway protective reflexes (cough, swallow, vocal cord movement). Neostigmine or naloxone was given if necessary. The duration of surgery, amount of intraoperative fentanyl administration, and time to extubation were recorded.

All patients were transferred to the postanesthesia care unit (PACU). They were monitored for 90 minutes and received nasal oxygen supplementation. A loading dose of 0.5 mg/kg tramadol was administered for postoperative analgesia. Pain was evaluated with the VRS as soon as the patients were responsive to verbal stimuli. Tramadol boluses of 0.5 mg/kg were given to achieve a VRS score of $\leq$4 at 5-minute intervals by an independent anesthetist in the PACU and thereafter as required by an independent nurse on the ward. Postoperative analgesia was considered insufficient if the VRS score exceeded 8 or remained >4 for 15 minutes, and flurbiprofen axetil (50 mg) was administered as an additional analgesic.

Sedation was rated with the Ramsay scale as follows: 1, anxious and agitated; 2, cooperative and