Journal of Clinical Anesthesia 41 (2017) 30–34

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

Original Contribution

Effect of parecoxib sodium pretreatment combined with dexmedetomidine on early postoperative cognitive dysfunction in elderly patients after shoulder arthroscopy: A randomized double blinded controlled trial

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ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 22 May 2017
Accepted 12 June 2017
Available online xxxx

Keywords:
Cyclooxygenase-2 inhibitor
Dexmedetomidine
Postoperative cognitive dysfunction
Brain
Pain
Elderly

ABSTRACT

Study objective: To evaluate effect of parecoxib sodium pretreatment combined with dexmedetomidine on early postoperative cognitive dysfunction in elderly patients after shoulder arthroscopy.
Design: Randomized, double-blind study.
Setting: University-affiliated teaching hospital.
Patients: One hundred and fifty-two elderly patients scheduled for shoulder arthroscopy.
Interventions: At 15 min before the induction of anesthesia, 152 patients received intravenously parecoxib sodium 40 mg and dexmedetomidine at a dose of 0.5 μg/kg over 15 min, followed by a continuous infusion at a rate of 0.5 μg/kg/h until the end of surgery. Then all patients who received postoperative patient-controlled intravenous analgesia were divided 2 groups: sufentanil(0.04μg/kg/h, S group), sufentanil (0.04μg/kg/h) plus dexmedetomidine(0.06μg/kg/h) (SD group).
Measurements: The mini–mental status examination score in SD group was significantly higher than S group at 1, 2 and 7 days after surgery. The incidence of postoperative cognitive dysfunction during 7 days after surgery in S and SD groups was respectively 17.1% and 6.7%. Compared with the S group, the visual analogue scale scores at rest and upon movement were significantly lower at 6, 14, 24, 36 and 48 h after surgery in SD group; analgesia pump liquid amount during 24 h after surgery and number of rescue analgesia during 48 h after surgery were significantly lower in SD group. Jugular venous oxygen partial pressure and jugular venous oxygen saturation values in SD group were significantly higher than S group at postoperative 24 h. The occurrence of nausea and vomiting within 48 h after surgery in SD group were significantly lower than S group. We found no complications including respiratory depression and sinus bradycardia within 48 h after surgery in all patients.
Conclusions: Parecoxib sodium pretreatment combined with dexmedetomidine could reduce the incidence of early postoperative cognitive dysfunction in elderly patients. This might be related to the improvement of postoperative analgesia effect and cerebral oxygen metabolism in patients.

1. Introduction

Shoulder arthroscopy is one of the effective means of treatment shoulder surgery. But due to the shoulder is a special part, in which tourniquet could not be used. In order to maintain a clear operative field and reduce bleeding, there is a need for intraoperative controlled hypotension and intra-articular pressure washing [1]. However, intraoperative cerebral blood flow reduction and postoperative acute pain are easy to induce postoperative cognitive dysfunction in elderly patients with degenerative changes of brain cells.

Postoperative cognitive dysfunction (POCD) is a common complication of central nervous system in elderly patients, and POCD has been shown to be temporary cognitive decline associated with the surgery [2]. POCD is not only related to the anesthetic and surgery-related factors [3–4], but also related to acute postoperative pain [5]. Acute postoperative pain management technique is an important risk factor of POCD, and appropriate management techniques that alleviate postoperative pain can improve postoperative cognitive function in patients. Parecoxib sodium is a highly selective cyclooxygenase-2 (COX-2) inhibitor. Studies have shown that parecoxib sodium preventive analgesia could enhance analgesic effects [6–7]. Dexmedetomidine is a specific a2-adrenergic receptor agonist, which has analgesic, sedative and

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http://dx.doi.org/10.1016/j.jclinane.2017.06.004
0952-8180/

hypnotic, anxiolytic effects. Studies have found that dexmedetomidine had brain protective effects [8–9], it could also enhance the analgesic effect of opioids [10]. However, the mechanisms of their action are different, it remains unclear whether the combination has a synergistic effect. This study was designed to investigate the effect of the pre-administration of parecoxib sodium combined with dexmedetomidine on early postoperative cognitive function in elderly patients after controlled hypotension shoulder arthroscopy and to observe the adverse events during 48 h of after surgery.

2. Materials and methods

2.1. Patients and study design

The protocol was approved by the Ethics Committee of Jiaxing the Second Hospital (Jiaxing, China). The study was conducted in accordance with the guidelines of Good Clinical Practice and the principles expressed in the Declaration of Helsinki. The study was registered at chictr.org(ChiCTR-INR-17010347). Each patient signed an informed consent for participation.

From June 2013 to May 2016, patients who were undergoing elective shoulder arthroscopy, according with American Society of Anesthesiologists (ASA) grade II–III, ≥60 years old were selected, and received 48 h patient-controlled intravenous analgesia (PCIA) after surgery for this study. The patients were randomly divided into two groups (n = 76 each) by an independent anesthetist. The patients and investigators were not informed of the groupings of the patients. Exclusion criteria: the patients refused to participate, patients with a history of neurological and psychiatric disorders, patients who take psychotropic drugs, patients with a history of alcohol abuse or drug dependence, patients who often use pain medications, patients who receive opioid and dexmedetomidine for allergies, patients with mini–mental status examination (MMSE) scores <23, patients with chronic obstructive pulmonary disease, patients with a history of heart block or sinus bradycardia.

2.2. Anesthesia management

All patients had no premedication. After arriving at the operating room, all patients were monitored using 5-lead electrocardiography(ECG), noninvasive blood pressure (NIBP), pulse oximetry (SpO_2), partial pressure of end-tidal CO_2 ($PetCO_2$), and temperature. After local anesthesia, an arterial cannula was placed in the left or right radial artery to monitor invasive arterial blood pressure. The electrodes of the bispectral index (BIS, Aspect, USA) was placed on the side of the patient's forehead to measure the depth of sedation. At fifteen minutes before the induction of anesthesia, parecoxib sodium 40 mg (Batch number: J20130044, Pharmacia and Upjohn Inc., USA) diluted with 5 ml of saline was intravenously injected in patients in every group. At the same time, dexmedetomidine was intravenously infused at a loading dose of 0.5 μg/kg over 15 min, followed by a continuous infusion at a rate of 0.5 μg/kg/h until the end of surgery in two groups, (Batch number: 13071134, Jiangsu HengRui Medicine Co., Ltd). Anesthesia was induced by intravenous administration of midazolam (0.04 mg/kg), propofol (1.5–2 mg/kg), sufentanil (0.4–0.6 μg/kg), and cisatracurium (0.2 mg/kg). Patients underwent endotracheal intubation for mechanical ventilation, with a tidal volume of 8–10 ml/kg, respiratory rate of 12–14 times/min, inspiratory to expiratory ratio of 1:2, and $PetCO_2$ was maintained at 35–45 mm Hg (1 mm Hg = 0.133 kPa). After endotracheal intubation, under the guidance of ultrasound, the intrescalene brachial plexus block was performed, 0.375% ropivacaine 20 ml was used for the block and the block was one shot, and right internal jugular vein catheter was retrogradely placed to the external auditory canal level (internal jugular bulb) to prepare for blood sampling. All patients were in lateral position.

Intravenous infusion of propofol (4–8 mg/kg/h) and cis-atracurium (0.1–0.2 mg/kg/h), and remifentanil (0.05–0.25 μg/kg/min) was adjusted according to MAP in operation. BIS values were maintained at 40–55. Arterial pressure transducers was placed in the external auditory canal level. Mean arterial pressure (MAP) was maintained at 60–65 mm Hg, but for patients with a history of hypertension, MAP was decreased to a baseline of 75–80%. MAP was lower than 55 mm Hg or MAP decreased to <30% of the baseline values in patients with a history of hypertension, phenylephrine was administered, while 0.5 mg atropine was given if the HR fell to <50 bpm. The treatments were repeated if necessary. Nasopharyngeal temperature was maintained ≥36 °C. At the start of skin closure time, all intravenous infusion anesthetics were stopped; and the analgesia pump was connected. Before connecting analgesia pump, 0.06 μg/kg of sufentanil was intravenously injected. Postoperative analgesics were used for PCIA. Operative time, transfusion volume, urine volume, and recovery time were recorded. The occurrence of hypotension and sinus bradycardia were also recorded.

2.3. Postoperative pain management

The degree of pain at rest and upon movement was measured at 1, 3, 6, 14, 24, 36 and 48 h after surgery using the 11-point numerical the visual analogue scale (VAS) (0 = no pain, 10 = most severe pain). Analgesia pump parameters were set to a background flow of 2 ml/h, PCA 1.5 ml, and a lockout time of 5 min, maximal 6 ml/h. If the patient's rest VAS score is ≥4, 2 ml of analgesia pump liquid was given by the investigator.

2.4. Endpoints

The primary outcome measures were mini–mental status examination scores 1 day before surgery and 1, 2 and 7 days after surgery and the occurrence of post-operative cognitive dysfunction during 7 days after surgery in the two groups. The secondary outcome measures were jugular venous oxygen partial pressure and jugular venous oxygen saturation, pain intensity, analgesia pump liquid amount within 24 h after surgery and number of rescue analgesia during 48 h after surgery, level of sedation and concerning adverse effects.

At preoperative 1 day and postoperative 1, 2 and 7 days, MMES score was used to evaluate cognitive function, which was defined according to the MMSE score [11]. MMSE score out of 30 points, postoperative MMSE score was ≤2 points compared with preoperative baseline to reflect POCD [12]. POCD incidence was recorded within seven days postoperative.

At immediately controlled hypotension, controlled hypotension 1 h, postoperative 24 h, blood samples was taken from the radial artery and internal jugular vein bulb for blood gas analysis. Arterial blood lactic acid(LAC), base excess(BE), arterial oxygen saturation(PaO_2), jugular venous oxygen partial pressure($PjvO_2$) and jugular venous oxygen saturation($SjvO_2$) values were measured and recorded.

Ramsay score was used to assess the level of sedation (1 points: anxiety; 2 points: quiet cooperation with directional force; 3 points: sleepiness, but the order reaction; 4: sleeping, quick response to tapping theglabella and loud auditory; 5: sleeping, delayed response to tapping theglabella and loud auditory; 6 points: deep sleep state, it is difficult to wake up). The degree of pain at rest and upon movement was measured at 1, 3, 6, 14, 24, 36 and 48 h after surgery using the 11-point numerical the visual analogue scale (VAS) (0 = no pain, 10 = most severe pain). The 24-h analgesia pump liquid amount was recorded, the occurrence of nausea and vomiting, itching, shiver, respiratory depression and sinus bradycardia were observed within 48 h after surgery.

2.5. Statistical analysis

The sample size was calculated on the basis of our preliminary experiments difference of 20% in the incidence of POCD during 7 days after surgery. For a study power of 90% ($\alpha = 0.05, \beta = 0.1$), the required