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Original Contribution

The effect of the timing and dose of dexmedetomidine on postoperative delirium in elderly patients after laparoscopic major non-cardiac surgery: A double blind randomized controlled study

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ABSTRACT

Study objective: There were few clinical data dosing and timing regimen for preventing postoperative delirium. The present study aimed to investigate the effect of the timing and dose of dexmedetomidine on postoperative delirium in elderly patients after laparoscopic major non-cardiac surgery.

Patients and interventions: A total of 354 patients > 65 years of age undergoing laparoscopic major non-cardiac surgery under general anesthesia received a dexmedetomidine 1 μg/kg bolus followed by 0.2–0.7 μg/kg/h infusion from induction of anesthesia to the end of surgery [group D1]); a dexmedetomidine (1 μg/kg bolus [group D2]); or saline (group S) 15 min before the end of surgery.

Measurements: The incidence and duration of delirium for 5 days after surgery and the cytokine (tumor necrosis factor-alpha TNFα, interleukin [IL]-1 β, IL-2, IL-6, IL-8, and IL-10) and cortisol levels were measured 1 h and 24 h after surgery.

Main results: Group D1 reduced incidence and duration of delirium and group D2 decreased its duration in patients with delirium compared to group S. IL-6 levels were significantly lower at 1 h and 24 h after surgery in group D1 than in group S, and lower at 24 h after surgery than in group D2. IL-6 levels in group D2 were significantly lower only at 1 h after surgery than in group S. However, IL-6 levels in delirious patients in group D2 were significantly lower at 1 h and 24 h after surgery than those in group S. Cortisol levels 1 h after surgery were significantly lower in groups D1 and D2 than in group S.

Conclusions: The dose and timing of dexmedetomidine appeared to be important in preventing delirium. The reduced incidence and duration of delirium by dexmedetomidine was associated with reduced levels of IL-6 24 h after surgery.

1. Introduction

Postoperative delirium in elderly patients undergoing major surgery including cardiac surgery, is a relatively frequent and serious complication [1–4]. Postoperative delirium is distressing to patients, caregivers, and medical staff, and has been associated with higher morbidity and mortality, cognitive dysfunction, prolonged hospitalization, and increased healthcare costs. Zhang H et al. reported the strategies for prevention of postoperative delirium [5].

Although postoperative delirium is precisely defined and a lot of diagnostic and evaluation tools are available, its pathophysiology remains still poorly understood. Previous studies have reported that sedation with the α_2-adrenergic agonist dexmedetomidine was associated with a lower incidence, duration, and severity of postoperative delirium [3,5].

Many studies have been shown that dexmedetomidine inhibits the neuroendocrine and inflammatory response in various animal and human studies [6–8]. The neuroendocrine and inflammatory responses to surgery are believed to be responsible for postoperative delirium [9–13].

Although dexmedetomidine has demonstrated its effectiveness in preventing delirium, its use remains controversial [14]. Moreover, supporting clinical data from well controlled studies regarding the optimal timing and dosing schedule of dexmedetomidine has yet to be

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established. Su et al. [15] recently reported that randomized, blinded study of low dose, non-titrated dexmedetomidine in old patients admitted to ICU immediately after operation. The dosing regimen (0.1 μg/kg/h) used in their study was a very low dose, well below that used for sedation in most patients, which reduced as well incidence of postoperative delirium as primary endpoint as secondary outcomes (subjective sleep quality, pain, daily prevalence of delirium, time to extubation, and length of ICU stay.

Therefore, we hypothesized that various dexmedetomidine dosage and timing regimens would vary the concentration of stress hormones and systemic inflammatory response to surgery. The changes in the concentrations of stress hormones and inflammatory mediators released in response to surgery would be affected the incidence and duration of postoperative delirium.

2. Methods

2.1. Study design

We obtained ethical approval for the present study (Registration No. 3001) from institutional review board in April 2016, and informed written consent from all participants. Our study also was listed on the ISRCTN registry with study ID ISRCTN85517037. The study was performed at University Hospital from May 2016 to May 2017. A total of 354 patients > 65 years of age, classified as class I or III according to the American Society of Anesthesiologists (ASA), who scheduled for laparoscopic major non-cardiac surgery under general anesthesia were enrolled in this study.

Patients with a history of kidney or liver disease, history of allergy to the drug being studied, cognitive impairment, use of antipsychotic alpha-2 agonists or antagonist medications, or use of anti-inflammatory drugs were excluded from the study. 354 patients in present study were included for eligibility and each group received study medication after randomization. 36 of the patients initially enrolled were withdrawn from the study because of loss of follow-up, conversion of laparoscopic to open surgery, or re-exploration for postoperative complications such as bleeding (Fig.1.).

2.2. Randomization and procedures

Randomization sequence was created using Stata 9.0 (StataCorp, College Station, TX, USA) statistical software and was stratified by center with a 1:1 allocation using random block sizes of 6. Participants were randomly assigned following simple randomization procedures (computerized random numbers) to 1 of 3 treatment groups: group D1 (n = 118) received dexmedetomidine (1 μg/kg bolus followed by 0.2 to 0.7 μg/kg/h infusion from induction of anesthesia to the end of surgery); group D2 (n = 118) received dexmedetomidine (1 μg/kg diluted to a total volume of 10 mL in saline [0.9%] over a 10 min period) 15 min before the end of surgery, and group S (n = 118) received an equivalent volume of saline 15 min before the end of surgery.

The dosage was used as the does recommended by the company. The starting load is 1 μg/kg bolus and maintenance dose is 0.2 to 1 μg/kg/h which is dependent on the sedation situations. Patients were blinded to the anesthetic agent; however, anesthesiologists and nurses were not because they needed to adjust the timing and dose of dexmedetomidine. The researchers who assessed the outcomes were, however, blinded.

2.3. Anesthesia and perioperative care

All patients were not premedicated before arriving to the operating room. The patients were monitored by pulse oximeter, automated blood pressure, urinary catheters, electrocardiogram, and end-tidal CO_2 devices as part of the patients' management.

The anesthesia was induced with propofol (2 mg/kg) and rocuronium (0.9 mg/kg) and maintained with desflurane in all groups. We adjusted desflurane concentration according to mean arterial blood pressure (MBP) ± 20% and heart rate ± 20% and maintain bispectral index (BIS) between 40 and 60.

Neuromuscular blockade was reversed using pyridostigmine and glycopyrrolate when surgery was completed and the train-of-four (TOF) ratio had returned to 25%. When patients started spontaneous breathing and BIS values reached 80, extubation was performed.

Patient-controlled analgesia (PCA) pump containing morphine (60 mg), ketorolac (150 mg), and ramosetron (0.6 mg) in a total volume of 100 mL of saline was set to deliver a basal infusion of 2 mL/h and bolus doses of 0.5 mL, with a 15-min lockout period for postoperative analgesia. Postoperative pain intensity was measured using a 100 mm linear visual analog scale (VAS). The VAS score for pain was measured during movement at 24 h after surgery.

2.4. Neurobehavioral assessment

Patients were then moved to the postanesthesia care unit after extubation and evaluated every 5 min by blinded investigators based on discharge criteria and pain scores. Assessment of delirium with confusion assessment method (CAM) was performed preoperatively

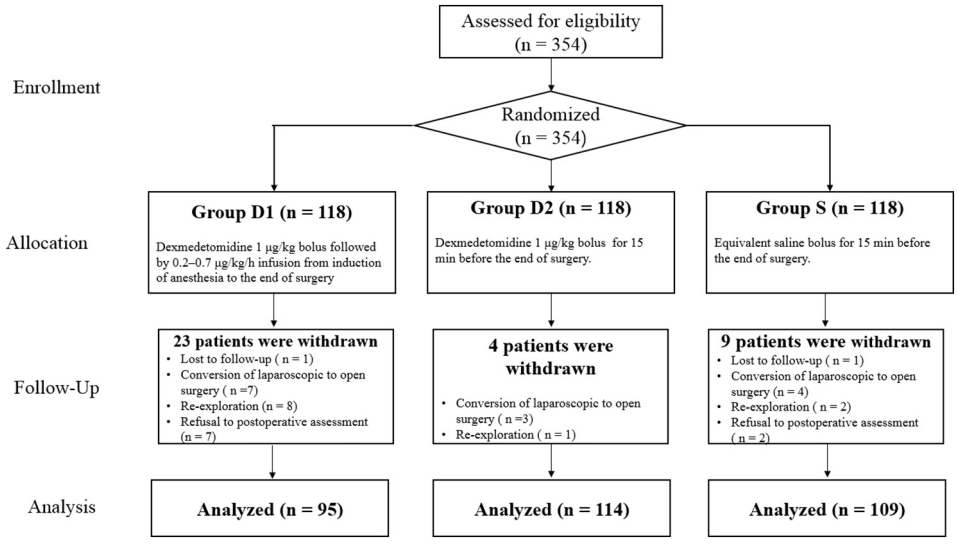

Fig. 1. Consort diagram.