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A comparison among infusion of lidocaine and dexmedetomidine alone and in combination in subjects undergoing coronary artery bypass graft: A randomized trial ☆

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ABSTRACT

Background: Previous studies have reported the cardioprotective effect of dexmedetomidine and lidocaine. We compared the effect of lidocaine and dexmedetomidine infusion during off-pump coronary artery bypass graft (OPCAB).
Methods: 153 patients undergoing OPCAB were enrolled. The lidocaine group (n = 36, Group LIDO) received an infusion of lidocaine 2 mg/kg/h after bolus 1.5 mg/kg; the dexmedetomidine group (n = 40, Group DEX) received dexmedetomidine 0.3–0.7 μg/kg/h; the combined group (n = 39, Group Combined) received infusion of both drugs; and the control group (n = 38) received nothing. We measured serum creatinine kinase-myocardial band (CK-MB) and cardiac troponin I (cTnI) concentration before and immediately after the surgery, postoperative day (POD)#1 and #2. The complication rate and clinical outcomes were compared.
Results: The concentration of cTnI was significantly lower in the Group LIDO and Group Combined than the control group on POD#2. The concentration of CK-MB was significantly lower in the Group LIDO and Group Combined compared to the control group on POD#1 and #2 [CK-MB on POD#1: 7.67 (5.78–11.92) vs. 7.18 (5.01–11.72) vs. 13.19 (6.85–23.87) in the Group LIDO, combined and control, respectively, Group LIDO vs. control: p = 0.003, Group Combined vs. control: p = 0.015]. The AUC of CK-MB was significantly lower in the Group LIDO and Group Combined than the control group. However, clinical variables including complication rate, ICU stay and one-year mortality were not different.
Conclusions: Lidocaine infused at 2 mg/kg/h, but not dexmedetomidine infused at 0.3–0.7 μg/kg/h reduced postoperative myocardial injury marker levels compared with the control group. However, no other clinical benefits were observed.

1. Introduction

In addition to having an antiarrhythmic effect [1,2], lidocaine has been reported to protect the myocardium from ischemia and reperfusion injury in animal studies [3–6] and lidocaine infusion during off-pump coronary artery surgery has been shown to reduce myocardial injury [7]. Dexmedetomidine has also been reported to have a cardioprotective effect in animal studies [8,9], although this has not been proven in a clinical study [10]. Dexmedetomidine inhibits the sympathetic activity

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by postsynaptic activation of α_2 adrenoceptors in the central nervous system, which decreases the neuroendocrine stress response [11,12]. Thus, both lidocaine and dexmedetomidine have potential beneficial effects of myocardial protection and reduction in arrhythmia incidence.

No clinical study has compared the infusion of lidocaine and dexmedetomidine in patients undergoing cardiac surgery. We hypothesized that lidocaine and dexmedetomidine would provide similar hemodynamic profiles and reduce the degree of myocardial injury and incidence of hypokalemia or arrhythmia in patients undergoing coronary artery bypass graft (CABG). We also attempted to evaluate whether combined infusion of lidocaine and dexmedetomidine has possible additive or synergistic effects, because a previous study reported combined neuroprotective effects of lidocaine and dexmedetomidine after forebrain ischemia in rats [13]. In this prospective randomized trial, the cardioprotective effect and clinical variables including the incidence of complication and mortality rate were compared between lidocaine, dexmedetomidine alone and their combined infusion.

2. Materials and methods

This prospective, single-blinded, randomized controlled study was approved by the Institutional Review Board of our institution and the study protocol was registered at http://www.clinicaltrials.gov (NCT01688648).

After obtaining written informed consent, patients undergoing off-pump coronary artery bypass (OPCAB) by a single surgical team were enrolled. Exclusion criteria included a surgery with pre-planned cardiopulmonary bypass (CPB), and patients diagnosed with arrhythmia with medication or pacemaker. A case with unexpected conversion to CPB during the surgery was excluded from the study.

Subjects were randomly assigned at a 1:1:1:1 allocation ratio into one of four groups, Group LIDO, Group DEX, Group Combined or control group, using the random numbers generated by an internet-based computer program (www.randomizer.org) and sealed envelope technique. The attending anesthesiologists opened the envelope and infused the study drugs. While the anesthesiologists were not blinded to the study drug, the participants, surgeon, and data analyst were kept blinded to the assigned group.

N.P.O. was started at midnight prior to surgery. Lactated Ringer's solution was administered during N.P.O. at a rate of 2.0 ml/kg/h, and was continued during the surgery, along with normal saline solution at a starting rate of 2.0 ml/kg/h. We did not premedicate the patients. The infusion rate of crystalloid and colloid solutions was adjusted to maintain the pulmonary capillary wedge pressure between 8 and 16 mm Hg according to the baseline values. Colloid solution was infused to compensate for the amount of blood loss collected by a cell salvage device. Salvaged blood by the cell salvage device was re-infused to the patient before the end of surgery. Packed red blood cells were transfused when the hematocrit level was less than 25% during the surgery.

Upon arrival in the operating room, standard monitoring devices were applied including a pulmonary artery catheter (Swan-Ganz CCOmbo CCO/SvO_2™, Edward Lifesciences LLC, Irvine, CA, USA). After a right radial arterial catheter was inserted for blood pressure monitoring, general anesthesia was induced with etomidate (0.2 mg/kg), sufentanil (1–2 μg/kg) and rocuronium (0.8 mg/kg) and then maintained with 0.8–1.0 minimum alveolar concentration of isoflurane in all groups. The isoflurane concentration was strictly controlled within the range. Vecuronium was infused continuously to make train-of four (TOF) count of 0 to 1 during the surgery. Tidal volume was initially set at 8 ml/kg of ideal body weight and lowered down to 6 ml/kg, while internal mammary artery grafting was performed to provide enough visual field for the surgeon. The respiratory rate was adjusted to maintain arterial carbon dioxide tension ($PaCO_2$) at 35–45 mm Hg strictly by the attending anesthesiologists. In all groups, remifentanil (10 μg/ml, Ultiva®, GlaxoSmithKline, Seoul, Republic of Korea) was infused at a dose range of 0.05–0.30 μg/kg/min during the surgery.

For the lidocaine infusion group (Group LIDO), lidocaine was infused at a dose of 2 mg/kg/h from the start of anesthesia induction after a bolus dose of 1.5 mg/kg. In the dexmedetomidine infusion group (Group DEX) dexmedetomidine (4 μg/ml, Precedex®, Hospira Korea, Seoul, Republic of Korea) was infused with a starting dose of 0.3 μg/kg/h. The dexmedetomidine infusion dose was adjusted within a range of 0.3–0.7 μg/kg/h to maintain a mean blood pressure (MBP) within 20% of preoperative value. Both lidocaine and dexmedetomidine were infused until 24 h after the end of surgery on postoperative day one (POD #1). Lidocaine and dexmedetomidine were both infused in the combined infusion group (Group Combined). Neither lidocaine nor dexmedetomidine was infused in the control group.

The measurements performed in this study are presented in Fig. 1. Arterial blood gas analysis (ABGA), including serum electrolyte measurement, was performed at five time points; just before the anesthetic induction, during air breathing (T1), at the end of anesthesia induction (T2), after internal mammary artery dissection and graft formation (T3), after the anastomosis of coronary graft (T4), and immediately after the operation in the ICU (T5). A blood sample for measurement of gas tensions and serum potassium concentration was obtained from an indwelling arterial catheter. ABGA was conducted immediately with blood gas electrodes (Rapidlab 1265; Bayer Healthcare, Leverkusen, Germany). Heart rate, MBP, mean pulmonary artery pressure and cardiac output were also recorded at each time point.

Myocardial injury markers including cardiac troponin I (cTnI) and creatinine kinase-myocardial band (CK-MB) were measured before surgery, immediately after the surgery (within 4 h after surgery at ICU), and on the first and second postoperative days (POD #1, POD #2, 6 a.m. in the morning) and compared among groups. CK-MB levels were measured using the photometric method (DiaSys Diagnostic System GmbH, Holzhein, Germany) and cTnI levels were measured using immunometric technology (Chuanzhi Biomedical Products Corp., Taiyuan, China).

Administered cardiovascular active drugs and the amount of fluids infused, operation time, anesthetic time, amount of transfusion, estimated blood loss, length of ICU stay, postoperative left ventricular systolic function, postoperative complication rate and one-year mortality rate were evaluated.

3. Statistical analysis

A sample size of 37 subjects in each group was determined from a power analysis using cTnI levels as the primary