Journal of Clinical Anesthesia 43 (2017) 77–83

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

Original Contribution

Optimal blood pressure decreases acute kidney injury after gastrointestinal surgery in elderly hypertensive patients: A randomized study☆,☆☆,☆☆☆,☆☆☆☆

Optimal blood pressure reduces acute kidney injury

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ARTICLE INFO

Article history:
Received 4 July 2017
Received in revised form 14 September 2017
Accepted 15 September 2017
Available online xxxx

Keywords:
Mean arterial pressure
Acute kidney injury
Elderly patients
Chronic hypertension
Risk factors

ABSTRACT

Study objective: To determine the appropriate mean arterial pressure (MAP) control level for elderly patients with hypertension during the perioperative period.
Design: A prospective, randomized study.
Setting: Three teaching hospitals in China.
Patients: Six hundred seventy-eight elderly patients with chronic hypertension undergoing major gastrointestinal surgery.
Interventions: Patients were randomly allocated to three groups and the target MAP level was strictly controlled to one of three levels: level I (65–79 mm Hg), level II (80–95 mm Hg), or level III (96–110 mm Hg).
Measurements: The primary outcome was acute kidney injury (AKI) (50% or 0.3 mg·dL^{-1}increase in creatinine level) during the first 7 postoperative days. The secondary outcomes were perioperative adverse complications. Moreover, vasoactive agents were observed during surgery.
Main results: The overall incidence of postoperative AKI was 10.9% (71/648). AKI occurred significantly less often in patients with level II MAP control (6.3%;13/206) than in patients with level I (13.5%; 31/230) and level III (12.9%; 27/210) ($P < 0.001$) MAP control. Level II was associated with lower incidences of hospital-acquired pneumonia (6.7%; 14/206; $P = 0.014$) and admission to the intensive care unit (ICU) (4.4%; 9/206; $P = 0.015$) and with shorter length of stay in the ICU ($P = 0.025$) when compared with level I and level III. Use of norepinephrine, phenylephrine, and nitroglycerin was significantly higher for patients with level III MAP control than for patients with level I and level II MAP control ($P = 0.001$).
Conclusions: For elderly hypertensive patients, controlling intraoperative MAP levels to 80 to 95 mm Hg can reduce postoperative AKI after major abdominal surgery.

1. Introduction

Acute kidney injury (AKI) is a significant clinical problem with a high rate of mortality and morbidity that affects 7.5% of patients who undergo noncardiac surgery [1–3]. A recent study showed that surgical patients with postoperative AKI are eight-times more likely to die within 30 days after surgery [4]. A large, retrospective study of 3.6 million veterans who underwent major surgery showed that patients with postoperative AKI had more negative outcomes than patients without AKI. For instance, patients with postoperative AKI often had longer hospitalizations, higher rates of 30-day hospital readmission, and higher 1-year mortality rates [5]. Many risk factors have been proposed to contribute to the occurrence of postoperative AKI, such as preexisting renal

☆ The work was mainly conducted in department of anesthesia, Shaoxing People's Hospital, Shaoxing Hospital of Zhejiang University

☆☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Only department support the study. Only department support the study.

☆☆☆ The manuscript has not been published previously or submitted elsewhere.

☆☆☆☆ All studies have been approved by Shaoxing People's Hospital (Shaoxing Hospital of Zhejiang University), The Clinical Research Ethics Committee, Ethical approval No. 45, 2015 ethics. Written informed consent was obtained from each patient or their caregivers before the study.

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https://doi.org/10.1016/j.jclinane.2017.09.004
0952-8180/

dysfunction, obesity, type of surgery, intra-abdominal pressure, and perioperative hemodynamic goals [6]. However, none of these proposed risk factors had been shown to be the key contribution to the occurrence of postoperative AKI.

Perioperative hypotension was recently proposed as an important determinant of postoperative AKI [5,7]. A large retrospective study revealed that the risk of postoperative AKI is significantly increased in surgical patients with >1 min of mean arterial pressure (MAP) lower than 55 mm Hg and >5 min of MAP from 55 to 59 mm Hg [2]. Another single-center cohort study demonstrated that postoperative AKI was associated with >10 min of intraoperative MAP lower than 55 mm Hg and 11–20 min of MAP lower than 60 mm Hg [8]. Asfar et al. [9] conducted a multicenter study involving 776 septic shock patients and showed that a target MAP of 65–70 mm Hg for patients without prior chronic hypertension and MAP of 80–85 mm Hg for patients with previous hypertension significantly lowered the incidence of postoperative AKI and the need for continuous renal replacement. These findings highlight the important role of MAP in postoperative AKI; however, the heterogeneity of the study subjects in these previous studies prevented understanding the appropriate MAP level during the perioperative period for elderly patients.

We performed a prospective, randomized study to determine the appropriate intraoperative MAP management level for elderly patients with chronic hypertension. The risks of three intraoperative MAP levels, 65–79 mm Hg, 80–95 mm Hg, and 96–110 mm Hg, for postoperative AKI were separately evaluated. Furthermore, we hypothesized that one of three intraoperative MAP levels might be suitable for elderly hypertensive patients and significantly reduce AKI after surgery.

2. Materials and methods

2.1. Study design and ethics

This was a prospective, randomized, and open-label study conducted at three teaching hospitals in China. This study was registered at www.Chictr.org.cn (ChiCTR-ROC-15006892) on August 7, 2015, and it was performed between August 24, 2015 and August 24, 2016. Eligible patients were randomly allocated to one of the following three groups: MAP, 65–79 mm Hg; MAP, 80–95 mm Hg; and MAP, 96–110 mm H. The study protocol was approved by the institutional ethics committees. Signed informed consents were obtained from all participants or their relative caregivers. This study was overseen by an independent data and safety monitoring group to ensure the safety of the participants, the validity of the data, and the credibility of the study results. Furthermore, investigators who collected follow-up information were blinded to the intervention status. All analyses were performed by an independent senior statistician before the randomization code was broken.

2.2. Subjects

We recruited patients who had chronic hypertension (diagnosed by systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg in the absence of antihypertensive medications) and were scheduled for elective major gastrointestinal surgery (gastric cancer eradication surgery or colorectal cancer surgery) *via* either an open or a laparoscopic route. Patients were included in the study if all of the following criteria were met: 1) patients were 65–80 years old; 2) patients had American Society of Anesthesiologists (ASA) physical status grade I to III disease with a predicted surgery time >60 min; 3) no surgery for preexisting renal disease; 4) current left ventricular ejection fraction >50%; and 5) no sign of cardiac dysfunction. Patients were excluded from the study if any of the following were true: 1) patients used non-steroidal anti-inflammatory drugs during the past month; 2) patients had heart failure during the past 2 months; 3) patients had myocardial infarction during the past month (confirmed by blood-specific enzymes); 4) current severe pulmonary function insufficiency; 5) current intermediate to severe pulmonary hypertension; and 6) chronic kidney diseases or renal dysfunction (confirmed by previous physician's diagnosis). Detailed information regarding patients' adherence to the antihypertensive drug regimen or the adequacy of the antihypertensive treatment was obtained before recruitment.

2.3. Anesthesia protocol

All patients were intravenously injected with 1–3 mg midazolam 30 min before surgery. After entering the operation room, left radial artery catheterization guiding by Doppler ultrasound was performed under local anesthesia. The FloTrac/Vigileo system (MHD8; Edwards Lifesciences, Irvine, CA, USA) was used to obtain the cardiac output/cardiac index (CI), stroke volume (SV), stroke volume variation (SVV), and other hemodynamic parameters. A 16-G intravenous line was inserted into the right internal jugular vein under B-wave ultrasound guidance for fluid infusion and intermittent monitoring of central venous pressure (CVP).

The anesthesia induction agents were propofol (plasma concentration 4–5 $\mu g \cdot mL^{-1}$ under target controlled infusion), fentanyl (3–5 $\mu g \cdot kg^{-1}$), and *cis*-atracurium (0.15–0.2 $mg \cdot kg^{-1}$). These were maintained with continuous infusion of remifentanil (effect site concentration 6–8 $ng \cdot mL^{-1}$) and propofol (effect site concentration 3–4 $\mu g \cdot mL^{-1}$) by targeted controlled infusion. The depth of anesthesia was monitored by the bispectral index (Aspect Medical System, Saint Charles, USA) and its value was kept between 45 and 60. The *cis*-atracurium ($0.004\ mg \cdot kg^{-1} \cdot min^{-1}$) was continuously infused to optimize muscle relaxation during surgery.

2.4. Fluid therapy

To ensure the appropriate volume status of the patients, a constant 7- to 8-$mL \cdot kg^{-1} \cdot h^{-1}$ crystalloid bolus fluid infusion was executed to maintain SVV at 8–13% and urine output at >1.0 $mL \cdot kg^{-1} \cdot h^{-1}$ during surgery (Fig. 1) [10]. Consecutive patients received an additional bolus of crystalloid 1.0 $mL \cdot kg^{-1}$ for each fasted hour from 8:00 AM until anesthesia induction. For patients undergoing laparoscopic surgery, the pneumoperitoneum insufflation pressure was set at 10–14 mm Hg. The FloTrac/Vigileo device was used to measure SVV and other hemodynamic parameters; 200 mL 6% hydroxyethyl starch was induced within 15 min each time, with SVV between 10% and 13%, and monitored by the FloTrac/Vigileo system. When the measured SVV was 13% more than the normal level (lasting for 5 min), or when the current subset reaction was positive (SV increased >10%), an additional 200 mL 6% hydroxyethyl starch was introduced. Blood transfusion was performed to control hemoglobin levels > 90 $g \cdot L^{-1}$ according to perioperative blood transfusion guidelines [11], and intraoperative blood gas analysis was tested every 30 min during surgery. The body temperatures of all patients were maintained at higher than 36 °C using an insulation blanket.

2.5. MAP control protocol

Vasoactive agents such as noradrenaline (0.03–0.3 $\mu g \cdot kg^{-1}\ min^{-1}$), phenylephrine (10–100 μg each bolus), nitroglycerin (0.03–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and phentolamine (0.5–3 mg every bolus) were introduced to adjust the MAP level. The initial dose for continuous infusion of noradrenaline or nitroglycerin was 0.03 $\mu g \cdot kg^{-1}\ min^{-1}$. Noradrenaline and nitroglycerin were selected for continuous infusion, whereas phenylephrine and phentolamine were only used for bolus injections. If the current MAP deviated from the target goal, then it was corrected to the target level within 5 min using the aforementioned agents. If repeated bolus injections were used more than four times, and if the MAP level still could not be titrated to the target goal, then continuous infusion was initiated in increments or decrements of 0.03 $\mu g \cdot kg^{-1}\ min^{-1}$ for at least 3 min. The vasoactive agents were