

Study Protocol with SAP

Comparison of the effects of Norepinephrine and Phenylephrine on tissue oxygenation and hemodynamic stability during an SVV fluid guided therapy in elderly undergoing radical resection of colorectal carcinoma

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Introduction

Fluids management is crucial during the operation, it is a part of integrated and life-saving treatment. Different strategy of fluids management intraoperative has great influence on patient's outcome and overall morbidity and mortality. Conventional liberal fluid management often cause fluid overload, resulting in tissue swelling and cellular edema, and then patients will occur gastrointestinal tract and pulmonary complications, including nausea, vomiting, paralytic ileus and pulmonary edema or pneumonia, Even prolonged the hospitalization time and ICU stays, increasing medical costs; However, Restrictive fluid management leads to reduced of effective circulating blood volume, it also caused different problems such as circulatory abnormalities, resulting in an imbalance between systemic oxygen delivery and oxygen consumption, and even leads to global tissue hypoxia or shock. Therefore, the fluid overload or insufficient are not benefit to patients, "The right amount" of fluid to be infused remains a question.

Following the indicators monitored by esophageal ultrasound or other invasive monitoring techniques are widely used in clinically work, including cardiac output(CO)、stroke volume(SV)、stroke volume variation(SVV)、Pulse pressure variation(PVV) and pulse perfusion variation index (PVI), which can dynamically reflect volume responsiveness, the goal-directed fluid therapy(GDFT) in perioperative gradually caught our attention. GDFT is a individualized fluid treatment that based on the Frank-Starling law, the aim is to stabilize the indicators (SVV、PVV、PVI、CO) in the certain range through supplement capacity, to achieve the ideal of intravascular volume, then the cardiopulmonary function of patients is optimized and the optimal oxygen supply for tissue organs. The SVV is one of the commonly used indicators in GDFT, which based on the variations of stroke volume during the respiratory cycle.

Many studies have proved the effectiveness of GDT in guiding fluid therapy and better outcome mostly in critically ill and septic patients, rarely in elderly patients. In fact, people older than 65 years represent the fastest-growing segment of the population. Exponentially, the percentage of elderly presenting for Gastrointestinal surgery is enlarging. Due to the long periods of fasting, bowel preparation, surgical stress and pre-existing morbidities, especially in addition to the role of peripheral vasodilation caused by anesthetic drugs, elderly are more prone to dehydration and to perioperative hypotension. SVV GDT and colloid alone might not be able to correct hypotension for this group of patients, Thus it is imperative need for vasoconstrictors.

Phenylephrine and norepinephrine are commonly used in clinical practice to counteract arterial hypotension. Phenylephrine is a pure α 1 adrenoceptor agonist, predominantly resulting in vasoconstriction, whereas norepinephrine has both α 1 and β 1 adrenoceptor agonist properties, with additional positive inotropic and chronotropic effects. Although both agents are equally effective in restoring a desired blood pressure, their individual working mechanisms may have different consequences for the macro and microcirculation. Norepinephrine was more described in literature and preferred by clinicians while Phenylephrine was less talked about and was used in specific clinical settings.

Our impression was that phenylephrine might be as effective as norepinephrine in improving Hemodynamic variables and tissue oxygenation. **The aim of this study** was to test the hypothesis that phenylephrine could be as effective as norepinephrine in treating hypotension in elderly undergoing radical resection of colorectal carcinoma.

Materials and methods

Ethical approval for this study (Reference: 2016068) was provided by the Ethical committee of the Second Hospital of Dalian Medical University, Dalian, China on the 4th of August,2016). The trial was registered with the U.S.National Institutes of Health National Clinical Trials (NCT03215797).

Patients selection

Eighty (80) elderly aged over 65 years old undergoing radical resection of colorectal carcinoma surgery were planned to be enrolled in this study. So far, we have enrolled 68 patients from July 18, 2017 to January 18,2018. 35 patients in norepinephrine group and 33 patients in phenylephrine group.

Inclusion criteria were: Radical resection of colorectal carcinoma surgery; Age over 65 years old; Surgery time >2 hours; ASA II or III(the American Society of Anesthesiologists, ASA); Exclusion criteria were: Clear arrhythmia; Severe cardiovascular disease; Need to use positive end-pressure ventilation (PEEP); Peripheral vascular disease; Arterial catheterization contraindications. Patients were randomly divided into two groups: Group N (Norepinephrine 5ug/ml) and Group P (Phenylephrine 20ug/ml). The concentration of norepinephrine and phenylephrine were based on the efficiency of two drugs.

Preparation for anesthesia and hemodynamic monitoring

When patients arrive in the operation room, standard monitoring equipment was connected to them, including ECG, pulse oximeter and noninvasive blood pressure

monitor on the right upper arm. Then, the arterial puncture needle was inserted in left radial artery under local anesthesia and connected to the Flo Trac Vigileo, We can get the parameters, such as CI, CO, SVV, SV, and the invasive artery blood pressure. After intubation, A central venous catheter was inserted via the right internal jugular vein, it allows us to pump drugs and monitor central venous pressure.

Anesthetic Management

In both groups, standard general anesthesia was induced after 5 min mask oxygenation with 100% O₂, then i.v. fentanyl 4-7µg/kg, etomidate 0.15-0.3mg/kg, cisatracurium 0.15mg /kg. After tracheal intubation, the lungs were ventilated at 8 ml/kg of tidal volume in a volume-controlled mode with 0-3 mm Hg positive end-expiratory pressure. The respiratory rate was set to maintain the end-tidal carbon dioxide at 35-40 mm Hg. The ventilator settings were unchanged during this study. Anesthesia was maintained with dexmedetomidine given at a dose of 0.2-0.4ug/kg.h propofol 4-6mg / kg.h , 1-1.5 % sevoflurane and remifentanyl 0.25-0.5mcg / kg.h adjusted to maintain a bispectral index of 40-60. The body temperature was maintained at >36°C by a fluid warmer.

Experimental Protocol

Blood pressure should be maintained to be not less than 20 % of the basic values in intraoperative period. if the blood pressure was in normal range and SVV was less than 9(measured by the FloTrac/Vigileo 3.0), patients was given a continuous infusion of 5 ml/kg/h crystalloid solution (Ringer's acetate); However, when hypotension occurred and SVV was greater than 13, a bolus of 200cc colloid (Voluven 130/0.4; 6%) was fastly administered, if the blood pressure was not elevated to normal after 5mins, then norepinephrine or phenylephrine was injected through central catheter. When SVV was between 9-13, a bolus of crystalloid of 8ml/kg was administered. According to the previous study, the effective ratio of norpinephrine and phenylephrine is 1:20, so the concentration of norepinephrine and phenylephrine is 5ug/ml and 100ug/ml respectively. Heart rate was maintained not less than 20% of the baseline value, urine output maintained at 0.5 mL/kg/h, and CVP between 4 - 12 mmHg, if these value were exceed normal range, the corresponding remedies was given, such as atropine, diuretic. And dobutamine was infused in case this hypotension was accompanied with a decrease in cardiac output to less than 2.0L/min.

Parameters Investigated

Intraoperative observation index. Systematic hemodynamic parameters: MAP, HR, CO, CI, SV were recorded at some specified time points; the indicators that reflecting tissue oxygenation and perfusion, including DO₂I、VO₂I、ERO₂, Which were calculated based on the Fick equation, besides the ScvO₂ and Lac also were recorded at the beginning of operating and operating finished respectively; Moreover,

we also recorded the crystalloid, colloid , urine output, blood loss and the doses of dobutamine, vasoactive drugs, diuretics and atropine, which were used in surgery.

Postoperative observation index. When patients left the operating room, we counted the APACHE II scores of the first day after surgery and recorded the ICU stays, mechanical ventilation time, exhaust time, hospitalization time and expenses. we also compared the preoperative liver and renal function with postoperative 12 hours. In addition to recording the complications and the rate of death at 28 days.

Data registration and statistical analysis

Data were analyzed by SPSS 20.0 software. Normal distribution was assessed with mean \pm standard deviation. Within arms, data were assessed by using two-factor repeated measures analysis of variance. All two tailed tests were performed and statistical significance was defined as *P* value less than 0.05 in all cases. Data was imported into Microsoft Excel 2016 for synchronization and analysis.