27-11-2024

RESEARCH PROTOCOL:

Title

Effect of a VExUS (Venous Excess Ultrasound) guided protocol of perioperative fluid management on the incidence of postoperative pulmonary complications and postoperative acute kidney injury in patients undergoing thoracic surgery.

Introduction

Fluid Management in Thoracic Surgery

In thoracic surgery, intraoperative fluid management presents a challenge for anesthesiologists, as patients are at high risk of developing interstitial and alveolar edema of the lungs. A history of pulmonary disease, previous chemotherapy or radiation therapy in the area, one-lung ventilation, surgical manipulation, and ischemia-reperfusion injury can all damage the respiratory epithelium's glycocalyx, the alveolar epithelium, and surfactant, ultimately leading to pulmonary injury. These factors, combined with liberal perioperative fluid management, increase the risk of acute respiratory distress syndrome (ARDS), atelectasis, pneumonia, and ultimately postoperative mortality. Traditionally, a restrictive fluid management strategy is employed intraoperatively, with crystalloid administration at a rate of 1-2 ml/kg/h, ensuring that the perioperative fluid balance does not exceed 1500 ml. This restrictive strategy may increase the risk of hypovolemia, which can lead to tissue hypoperfusion, target organ dysfunction, and acute kidney injury. Within the Enhanced Recovery After Surgery (ERAS) protocols, goal-directed therapy (GDT) for fluid management in thoracic surgery is discussed but not explicitly recommended. Recommendations include avoiding overly restrictive or completely liberal fluid strategies, maintaining euvolemia, and preventing tissue hypoperfusion with balanced use of inotropic agents and fluid administration.

Postoperative Respiratory Complications

Pulmonary injury is the leading cause of death following thoracic surgery. Pre-existing respiratory disease, surgical manipulation, lung parenchyma resection, and the detrimental effects of one-lung ventilation increase the risk of postoperative respiratory complications. Although overhydration and ventilation with high tidal volumes have been replaced by a restrictive fluid strategy and the application of protective mechanical ventilation, it appears that all factors involved in ventilator-induced lung injury (VILI) also play a harmful role in one-lung ventilation. High strain on the ventilated lung, oxidative stress, surgical trauma, recruitment maneuvers, biological trauma, atelectatic trauma, and ischemia-reperfusion injury are the pathophysiological mechanisms leading to postoperative acute respiratory failure and, in 2-5% of cases, to ARDS.

Postoperative Acute Kidney Injury

Postoperative acute kidney injury (AKI) represents 18-47% of in-hospital AKI and is associated with prolonged hospitalization and high morbidity and mortality. Recently, the implementation of new AKI classifications (RIFLE, AKIN, KDIGO) has facilitated its early recognition for immediate preventive measures. Additionally, the detection of two early urinary biomarkers of kidney stress, the tissue inhibitor of metalloproteinases-2 (TIMP-2) and the insulin-like growth factor-binding protein 7 (IGFBP7), has contributed to this. Postoperatively, an increase in serum creatinine by up to 0.5 mg/dL from baseline has been associated with a threefold increase in mortality following cardiac surgery. Potential pathophysiological mechanisms of

postoperative AKI include ischemia, inflammation, and toxins. However, in thoracic surgeries, both the hypovolemia of a restrictive fluid administration strategy and overhydration and venous congestion can equally lead to acute kidney injury postoperatively.

VExUS Ultrasound Protocol

The VExUS protocol is a standardized point-of-care ultrasound examination that includes measurements of the inferior vena cava (IVC) diameter, combined with Doppler analysis of waveforms in the hepatic vein, portal vein, and renal veins. From this analysis, the presence of venous congestion—classified as mild or severe—or its absence is determined. A high VExUS score (grade 3) has been strongly associated with the occurrence of acute kidney injury in patients undergoing cardiac surgery and has more recently been linked to elevated right atrial pressure (RAP ≥ 12 mmHg). The protocol includes the following classification:

- Grade 0: IVC < 2 cm
- Grade 1: IVC ≥ 2 cm, with normal or mildly abnormal waveforms in the hepatic, portal, and renal veins (mild congestion)
- Grade 2: IVC ≥ 2 cm, with severely altered waveforms in at least one vein (moderate congestion)
- Grade 3: IVC ≥ 2 cm, with severely altered waveforms in multiple veins (severe congestion)

Study Aim

This study aims to investigate the effect of a VExUS ultrasound guided protocol of perioperative fluid management within a goal-directed therapy framework, on postoperative respiratory complications, and the occurrence of acute kidney injury in patients undergoing thoracic surgery.

The null hypothesis is that the application of VExUS during the perioperative period will not lead to a more judicious fluid administration strategy, avoiding an overly restrictive approach (control group), thus achieving the desired euvolemia in these patients (VExUS guided fluid management).

Method

Study Design

A single-center clinical study conducted in the Anesthesiology Clinic of the University General Hospital of Heraklion.

Parallel design in two groups.

Data analysis: primary analysis according to the "intention to treat" principle, supplementary analysis according to the "as treated" principle.

Inclusion Criteria

Adult patients over > 18 years undergoing video assisted thoracic surgery lobectomy under one-lung ventilation will be studied.

Exclusion Criteria

Patients will be excluded from the study if they:

- refuse to participate
- are scheduled for pneumonectomy

- are young athletes due to the likelihood of having an IVC > 2 cm as a normal variant
- exhibit moderate-severe tricuspid valve insufficiency, with moderate to severe pulmonary hypertension
- exhibit heart failure with reduced ejection fraction, EF<35%
- show portal hypertension, portal vein thrombosis, or liver cirrhosis
- have a history of stage 4 or end-stage kidney disease, with measured eGFR < 30 ml/min/1.73 m^2 or need for dialysis
- receive transfusion with more than 2 packed red blood cells units perioperatively

Conduct of the Trial

Basic Perioperative Care and General Monitoring

Preoperative assessment, fasting, and premedication according to the routine of the department:

- Discontinuation of fluid intake 2 hours before surgery
- cessation of food intake 6 hours preoperatively
- discontinuation on the day of surgery of ACE inhibitors, angiotensin receptor blockers, thiazide diuretics, and loop diuretics,

Upon entering the operating room, patients will be connected standard ASA monitors: 5 lead ECG, pulse oximetry (SpO2), non-invasive blood pressure measurement. Under local anaesthesia an arterial catheter will be placed for invasive blood pressure measurement and blood gas sampling, along with at least two venous catheters of 16-20 G. Anesthesia and postoperative analgesia management will depend solely on the discretion of the responsible anesthesiologist, within the framework of multimodal anesthesia-analgesia. After anesthesia induction and double-lumen endotracheal tube placement, patients will be connected to the anesthesia machine, recruitment maneuvers will be performed with PEEP titration, and they will be mechanically ventilated applying the principles of protective mechanical ventilation. The correct placement of the endotracheal tube will be confirmed with fiberoptic bronchoscopy immediately after placement. A urinary catheter will be placed for hourly urine measurement, along with a thermometer. Intraoperatively, the total administered fluids, hourly urine output, type and dose of vasopressor medications, and blood pressure (SAP, DAP, MAP) will be recorded every 15 minutes (unless a significant change occurs), along with arterial blood gases and lactate. Pulse contour analysis of cardiac output (CO,CI,SV,SVV) should be used, yet only for recording.

Protective Mechanical Ventilation of One Lung:

Ventilated lung:

- Tidal volume (Vt): 4-5 ml/kg ideal body weight
- Appropriate PEEP of 5-15 cmH2O, possible repeat of recruitment maneuver
- Plateau pressure - PEEP: up to 15 cmH2O
- Management of respiratory rate (RR) aiming for permitted mild hypercapnia (PaCO2 = 40-60 mmHg)
- Modification of the I ratio to avoid air trapping and the emergence of PEEPi
- Titration of FiO2 to achieve SpO2 = 88-92%

- Protection against hypoxic pulmonary vasoconstriction by avoiding vasodilators, hypoventilation, alkalosis, hypothermia, and if inhaled anesthetics are used, maintaining MAC < 1
- Mechanical ventilation model: Volume Control- Auto Flow on the Perseus A500 and Atlan A350 machines from Drager available in the Anesthesia Clinic

Non-ventilated lung with SpO2 < 88%:

- Recruitment maneuvers with the use of PEEP if possible
- Use of CPAP
- FiO2 = 100% and cessation of one lung ventilation

Control Group:
Intraoperatively patients of the control group will be administered isotonic crystalloids (Lactated Ringer's, Plasma-Lyte) at a rate of 3 mL/kg/h.
VExUS-guided Group:
VExUS Evaluation
The VExUS evaluation will be performed pre- and immediately post-intubation before one-lung ventilation initiation. A trained anesthesiologist (will evaluate the patient according to the VExUS protocol, measuring the IVC diameter and performing Doppler analysis of the hepatic, portal, and renal veins. A VExUS score will be assigned as outlined in the section above.
Ultrasound monitoring will be performed according to the VExUS protocol before positioning the patient in the lateral decubitus position. In patients with VExUS grade 0, a bolus of 250-500 mL (approximately 3 mL/kg) will be administered, followed by the infusion of crystalloids at a rate of 3 mL/kg/h. The inferior vena cava (IVC) diameter will be measured three times: once prior to anesthesia induction, once immediately after intubation, and once before patient emergence from anesthesia. In patients with VExUS grade 1, no bolus will be given, and only a fluid infusion at 3 mL/kg/h will be administered. In patients with VExUS grades 2 and 3, 10 mg of furosemide will be administered intravenously, followed by crystalloids infusion at a rate of 2 mL/kg/h.
In both groups, blood losses will be replaced with a 5% albumin solution at a 1:1 ratio, if hemorrhage exceeds 300 ml of blood. Transfusion will be administered to maintain hemoglobin levels at 9 mg/dL. Both groups will follow the same multimodal anesthesia-analgesia protocol, with restricted opioid use in accordance with the departmental routine.
Intraoperative hypotension (systolic arterial pressure < 90 mmHg or a decrease > 20% from baseline) will be managed with titrated norepinephrine infusion.

Post-Anesthesia Care Unit (PACU)
Control Group:
Fluid administration will continue at a rate of 3 mL/kg/h as per standard practice.
VExUS-guided Group:
VExUS ultrasound will be repeated postoperatively. In patients with VExUS grade 0, a bolus of 250-500 mL (approximately 3 mL/kg) will be administered, followed by the infusion of crystalloids at a rate of 3 mL/kg/h. In patients with grades 1 to 3, 10 mg of intravenous furosemide will be administered, followed by a fluid infusion at 3 mL/kg/h and reassessment.

Patients will be monitored daily for the occurrence of postoperative respiratory complications as defined by the European Society of Anaesthesiology. Preoperative blood gas values (PaO2, PaCO2) will be measured as baseline, and postoperative blood gases will be collected on the 1st and 3rd postoperative days in the PACU. Oxygenation will be assessed using the PaO_2/FiO_2 ratio, and lactate levels will be measured concurrently.

Additionally, for each patient, estimated glomerular filtration rate (eGFR) will be calculated preoperatively and on the 1st and 3rd postoperative days in PACU. To assess acute kidney injury (AKI), serum creatinine will be measured on the 1st and 3rd postoperative days, and AKI diagnosis and classification will follow KDIGO (Kidney Disease Improving Global Outcomes) criteria.

The following kidney injury biomarkers will also be measured:

- Serum and urine cystatin C
- Total urine protein and albumin
- Urine creatinine
- Kidney stress biomarkers TIMP-2 and IGFBP7 in urine, as described above, will be measured immediately postoperatively in the PACU or ward.

These biomarkers will also be measured in the PACU and on the 1st and 3rd postoperative days.

Statistical Analysis

Data analysis will be performed using RStudio (R version 4.3.2). Descriptive statistics will include mean and standard deviation or median and interquartile range, depending on the distribution of each variable.

The primary analysis will focus on the incidence of postoperative respiratory complications and acute kidney injury (AKI) between the two groups, using multivariable logistic regression. Adjustments for confounding factors will be made based on literature evidence linking these factors to the outcomes of interest.

Changes in quantitative variables (e.g., postoperative oxygenation, urea, creatinine, urine albumin) will be analyzed using repeated measures ANOVA. For non-normally distributed variables, the appropriate non-parametric tests will be applied. Statistical significance will be set at $\alpha = 0.05$.

Sample size calculations, assuming a 10% incidence of AKI in the control group and 5% in the intervention group, indicate that 115 patients per group are required for a power of 0.8 and a significance level of 0.05. An interim analysis will be conducted once 1/3 and 50% of the required sample size has been enrolled in the study.

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