

Perioperative Echocardiographic Hemodynamic Parameters and Postoperative Outcome in Pediatric Surgical Patients: A Descriptive Observational Prospective Pilot Study Protocol

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Abstract

Background: A randomized controlled trial (RCT) protocol in pediatric patients scheduled for surgery will be elaborated. In this RCT protocol trans-thoracic echocardiography will be realized perioperatively to guide fluid and hemodynamic therapy in these patients. This RCT will determine the impact of goal directed therapy with echocardiography on postoperative outcome in terms of morbidity, Length of Intensive Care Unit Stays (LOSICU), Length of Mechanical Ventilation (LMV), Length of Hospital Stays (LOS), fluid therapy and vasopressor-inotropic therapy. There are no trials in pediatric surgical patients which have identified echocardiographic hemodynamic parameters predictive of postoperative outcome in terms of morbidity, LOSICU, LMV and LOS. The objective of this pilot observational prospective trial protocol is to describe the study which will determine echocardiographic hemodynamic parameters predictive of postoperative outcomes. These hemodynamic parameters will be integrated in the RCT which has the objective to determine the impact of goal directed fluid and hemodynamic therapy guided by trans-thoracic echocardiography on postoperative adverse outcome.

Methods: Patients aged less than 18 years admitted for surgery will be included. Trans-thoracic echocardiography will be realized to measure different hemodynamic parameters perioperatively in included patients. Primary outcome will be postoperative morbidity, secondary outcomes will be LOSICU, LMV and LOS; tertiary outcomes will be fluid therapy, vasopressor and inotropic therapy. Primary outcome measure will be the presence of postoperative organ dysfunction. Secondary outcome measures will be the number of postoperative days spent in the Intensive Care Unit (ICU), number of postoperative days spent on invasive or non-invasive mechanical ventilation and the number of postoperative days spent in the conventional hospitalization ward. Tertiary outcome measures will be the quantity of fluid administered and the Vasopressor-Inotropic Score (VIS). The study will be monocentric. XLSAT 2018.3 or plus will be the software for statistical analysis. Results are expected in the first semester of 2022.

Conclusion: This pilot study will identify echocardiographic hemodynamic parameters predictive of postoperative adverse outcome which will be integrated in the second RCT where goal directed fluid and hemodynamic therapy will be guided with echocardiography.

Keywords: Pediatric surgery; Children; Echocardiography; Hemodynamics; Fluid therapy; Postoperative outcome

Introduction

Perioperative goal directed fluid and hemodynamic therapy (PGDFHT) has been studied in adults where it has demonstrated its efficacy in terms of reduced postoperative complications and length of hospital stay (LOS) [1-7]. The objective of PGDFHT is to monitor fluid responsiveness and hemodynamic status with the aim to improve oxygen delivery to different systemic organs and to improve tissular perfusion [8]. Tissular hypoperfusion can have side effects in terms of organ failure. Unoptimal fluid and hemodynamic status (insufficient or plethoric) can alter tissular perfusion. Therefore, monitoring fluid responsiveness and hemodynamic status using tools to assess adequate cardiac output to maintain sufficient tissular oxygen delivery is mandatory. There are no studies in children demonstrating the

impact of PGDFHT with echocardiography on postoperative outcome. However, there are studies in pediatric cardiac surgery mostly which identified perioperative biomarkers of postoperative adverse outcome [9].

These biomarkers were lactate levels, central venous oxygen saturation $SCVO_2$, regional cerebral, renal, splanchnic oxygen saturation and veno-arterial carbon dioxide gradient. Unoptimal values of these biomarkers predicted adverse postoperative outcome in terms of mortality, morbidity and length of hospital stay (LOS) [9]. Concerning the tool to assess cardiac output, fluid responsiveness and hemodynamic status, transthoracic echocardiography is a noninvasive mean which can bring solutions and some parameter like the variation of peak velocity at the aortic annulus has been validated to predict fluid responsiveness in children [10]. There are no studies which have clarified echocardiographic hemodynamic parameters predictive of postoperative outcome in children scheduled for surgery in general. Nevertheless, there is one retrospective study in pediatric and adult cardiac surgery which showed that intraoperative trans-esophageal echocardiography after surgical repair in congenital heart disease reduced LOS [11]. We have elaborated an RCT trial where fluid and hemodynamic therapy will be guided with trans-thoracic echocardiography. In this RCT echocardiography hemodynamic parameters will be integrated in a protocol to guide fluid, inotropic and or vasopressive therapy. To validate these echocardiographic hemodynamic parameters, we will conduct a pilot observational prospective study to identify those which are predictive of postoperative adverse outcome. We describe here this pilot trial. We have elaborated 2 similar protocols in pediatric patients with congenital heart disease [12,13]. We would like to generalize the protocol to other pediatric surgical patients. The primary objective of this study protocol is to describe the pilot trial which will be undertaken to identify echocardiographic hemodynamic parameters predictive of postoperative outcome in terms of morbidity.

The secondary objective is to clarify echocardiographic hemodynamic parameters predictive of postoperative LOS/ICU, LMV and LOS. The tertiary objectives are to determine echocardiographic hemodynamic parameters predictive of fluid therapy, vasopressor and inotropic therapy. The primary outcome measures will be postoperative organ dysfunction until discharge from hospital. The secondary outcome measures will be the number of postoperative days spent in the Intensive Care Unit (ICU), the number of postoperative days spent on invasive or noninvasive mechanical ventilation and the number of postoperative days spent in the conventional hospitalization ward. The tertiary outcome measures will be the quantity of postoperative fluid administered in terms of crystalloids, colloids, blood product and postoperative vasopressor inotropic score. Once the echocardiographic hemodynamic parameters predictive of postoperative outcome have been identified in this pilot study, they will be integrated in a randomized controlled trial which will determine the impact of intraoperative goal directed therapy with echocardiography in general pediatric surgery on postoperative outcome.

Methods and Materials

This trial has been declared at the French National Agency of Drugs and Medications Security, ANSM (National Agency for The Safety of Medicines and Health Products) and registered under the number RCB: 2019-A03256-51. After approval from the Ethics Committee, and after parents and or patient's information, patients will be included prospectively in one cohort. The patients included will be managed according to the usual local practices. Echocardiography Figure 1 will be realized in each patient perioperatively after induction of anesthesia. The echocardiographic hemodynamic parameters measured are precised below. The patients included will be children aged less than 18 years admitted for surgery or other intervention under anesthesia. General variables registered will be age, gender, type of surgery, elective or urgent surgery, American Society of Anesthesiologists status (ASA), weight, height, prematurity, blood pressure, heart rate, pulse oximetry and hemoglobin levels. Preoperatively basal values of blood pressure, heart rate, pulse oximetry, body temperature will be registered prior to anesthesia and surgery and intraoperatively during surgery hourly. Other intraoperative parameters registered are blood product transfusion (Packed Red Blood Cells (PRBC), Fresh Frozen Plasma (FFP), Concentrated Platelet Units (CUP), fibrinogen, cryoprecipitate, Concentrated Complex of Prothrombin (CPP) or other blood product derivatives, crystalloids and colloids or other fluids administered, blood loss, urinary output, quantity of inotropes, diuretics, anesthetic drugs administered and mechanical ventilation parameters, central venous pressure if monitored. Normal blood pressure and heart rate values are those defined according to the patient age [14]. In addition to echocardiographic hemodynamic parameters, postoperative variables registered once daily until discharge from hospital will be blood pressure, heart rate, core temperature, pulse oximetry, CVP if monitored, blood product transfusion (PRBC, FFP, CUP), fibrinogen, cryoprecipitate, concentrated complex of prothrombin, other blood product derivatives, crystalloids, colloids or other fluids administered, blood loss, urinary output, quantity of inotropes, diuretics, anesthetic drugs administered, mechanical ventilation parameters, hemoglobin levels. Trans-thoracic echocardiographic parameters measured perioperatively are described here after. Since echocardiography is operator dependent, all the echocardiographic hemodynamic parameters will be measured by one experienced medical doctor in pediatric echocardiography and validated by a second experienced medical doctor. Cardiac output measures will be realized with Velocity Time Integral (VTI) at the aortic valve in the apical five chamber view. Normal values of aortic VTI have been defined in children [15].

Fluid responsiveness will be assessed with aortic peak velocity at the apical five chambers view with peak velocity variation (ΔV_{peak}) of $\geq 10\%$ defining responders to fluid therapy. ΔV_{peak} is defined as $(V_{max} - V_{min}) / [(V_{max} + V_{min}) / 2] \times 100$ (10). Right ventricular (RV) and left ventricular (LV) systolic function will be assessed in the apical four chamber view with lateral S (Slat) wave velocity in tissue Doppler, with mitral and tricuspid annular plane systolic excursion (MAPSE, TAPSE) in time motion mode (TM) and with

ejection fraction EF with Simpson's method. Normal MAPSE, TAPSE and Slat values have been defined in children [16-21]. Fractional shortening (FS) will be assessed in the parasternal longitudinal axis view, normal values are the same as in adults (28-42%). Right ventricular and left ventricular diastolic function will be assessed in the apical four chamber view at the tricuspid and mitral valves

with pulsed Doppler to assess for E wave velocity, A wave velocity and E/A ratio. E/A ratios will be analyzed according to age [22-29]. To assess for normal, relaxation alteration, pseudonormal and restrictive profiles. Right and left filling pressures will be assessed with tissue Doppler at the apical four chamber view at the tricuspid and mitral valves to assess lateral E' wave velocity and E/E'lat ratio.

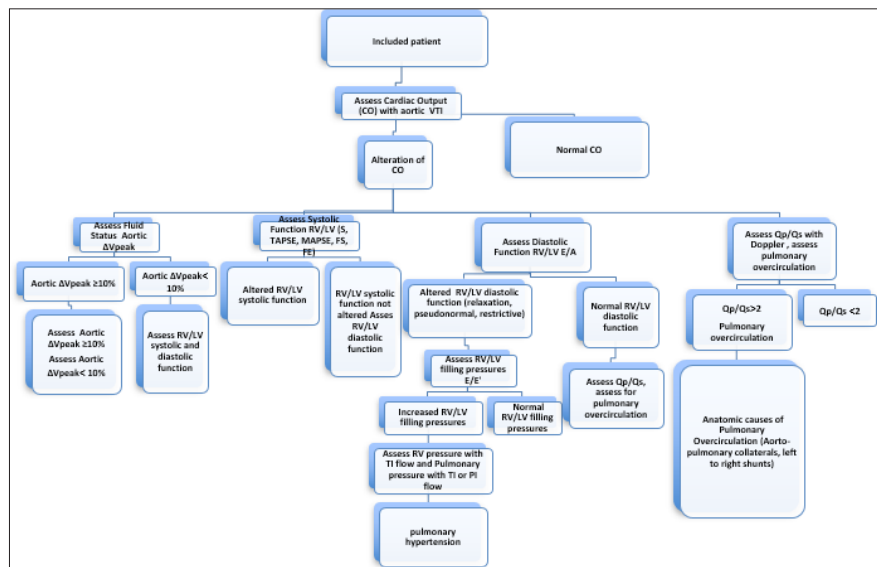


Figure 1. Echocardiographic hemodynamic parameters.

Normal E/E' and E'lat values have been defined in children [22-29]. To assess for pulmonary over circulation, Qp/Qs ratio (where Qp is pulmonary output and Qs is systemic cardiac output) will be calculated using the formula $Qp/Qs = \text{Pulmonary VTI} \times \text{Area of the pulmonary annulus} \times \text{HR} / \text{Aortic VTI} \times \text{Area of the aortic annulus} \times \text{HR}$. $\text{HR} = \text{VTI} \times \text{II} \times (D/2)^2 / \text{VTI} \times \text{II} \times (D/2)^2$, where D is the diameter of the annulus and HR the heart rate [30]. Pulmonary VTI and pulmonary annulus diameter will be assessed at the parasternal transverse axis view. Aortic VTI will be assessed at the apical 5 chamber view and the aortic annulus diameter at the parasternal longitudinal axis view. The inferior vena cava diameter (IVC) and the variation of the latter (ΔIVC) will be assessed at the subcostal view and will be defined as $\Delta\text{IVC} = [(D_{\text{max}} - D_{\text{min}}) / (D_{\text{max}} + D_{\text{min}} / 2)] \times 100$. Where D_{max} is the maximum and D_{min} is the minimum diameter of the IVC. Supra-hepatic Doppler waves velocity V, A, S, D and S/D ratios will be assessed in the subcostal view. Pulmonary Doppler waves velocity S, D, E, Ap and S/D ratios will be assessed in the apical four chamber view. Postoperative organ dysfunction until discharge from hospital will be registered to assess for primary outcome. The number of days spent in ICU, under invasive or noninvasive mechanical ventilation and days in the conventional hospitalization ward postoperatively will be registered to assess for secondary outcomes. The quantity of postoperative fluid (crystalloids, colloids, blood products) administered and postoperative vasopressor inotropic score will be registered to assess for tertiary outcomes. Statistical analysis will be realized with XLSTAT 2018.3 or plus software. Normally distributed and non-normally distributed variables will be compared using Student t or Mann-Whitney tests and Wilcoxon or Kruskal-Wallis tests respectively.

Normally distributed variables will be expressed in terms of means with standard deviation. Non normally distributed variables will be expressed in terms of medians with interquartile ranges. Categorical variables will be compared with the exact Fisher's test or Chi squared test accordingly. Categorical variables will be expressed as percentages with 95% confidence intervals. To assess for independent predictors of adverse postoperative outcome, multivariate analysis will be realized. A P-value ≤ 0.05 will be considered significant. Missing data will not be included. The study is expected to begin first semester of 2021 and will terminate end 2021. The number of patients included will be 1000 patients to have a normally distributed population. The study will be monocentric.

Result

Results are expected in the first semester of 2022.

Conclusion

This study protocol was designed to describe the pilot observational prospective trial which will identify echocardiography parameters predictive of postoperative outcome in terms of morbidity, LOSICU, LMV, LOS, fluid therapy and vasopressor inotropic score in children scheduled for surgery or other interventions. These echocardiographic predictors of the above-mentioned outcomes will be integrated in randomized controlled mono-multicentric trials which will determine the impact of intraoperative goal directed fluid and hemodynamic therapy with echocardiography on postoperative outcome in children scheduled

for surgery or other interventions under general anesthesia.

Disclosure

This study is part of the Thesis entitled 'Do goal directed therapies improve postoperative outcome in children? (Perioperative Goal Directed Fluid and Hemodynamic Therapy; Transfusion goal directed therapy using viscoelastic methods and enhanced recovery after surgery and Postoperative outcome)' [31-33]. This Thesis is registered online <http://www.theses.fr/s232762>.

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