International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 07, Issue 11, November 2022,
https://doi.org/10.23958/ijirms/vol07-i11/1553

Original article

Pulse Contour Cardiac Output System Monitoring in Pediatric Patients Undergoing Orthotopic Liver Transplantation

Zeynep Ersoy [1], MD, Zeliha Aycan Ozdemirkan [2], MD, Pinar Zeyneloglu [1], MD, Nedim Cekmen [1], MD, Adnan Torgay [1], MD, Zeynep Kayhan [1], MD, Mehmet Haberal [3], MD

[1]Baskent University, Faculty of Medicine, Department of Anesthesiology, Ankara, Turkey.
[2]Gazi University, Faculty of Medicine, Department of Anesthesiology and Critical Care, Ankara, Turkey.
[3]Baskent University, Faculty of Medicine, Department of General Surgery, Ankara, Turkey

*Corresponding Author: Zeynep Ersoy, MD; *zeynepsener2003@yahoo.com*

Received 25 October 2022; Accepted 15 November 2022; Published 18 November 2022

Abstract

Background: This study aimed to demonstrate that PiCCO monitoring can be early guidance for fluid monitoring and hemodynamic parameter analysis in the pediatric OLT population. ***Method:*** A single-centre, retrospective cohort study in pediatric patients who underwent OLT between September 2014 and October 2017. ***Results:*** Forty-one pediatric patients (aged 4 months to 17 years) underwent hemodynamic monitoring with PiCCO during OLT. Measurements including mean arterial pressure (MAP), central venous pressure (CVP) and cardiac index (CI) were significantly lower during the Tanhepatic phase when compared to Tbaseline and Tnewhepatic phases ($p<0.05$ for all). Among the patients whose mean of Tnewhepetic extravascular lung water index (EVLWI) measurements were more excellent than 7 mL/kg; more significant amounts of intraoperative blood transfused ($p=0.027$), higher graft recipient body weight ratio (GRWR) ($p=0.016$) and longer anesthesia times ($p=0.046$) were seen. The mean of Tnewhepatic stroke volume variability (SVV) measurements was greater than 10% in patients with a higher GRWR ($p=0.033$). More blood transfusion was needed and a higher GRWR was observed in patients with a global end-diastolic volume index (GEDVI)<650 ml/m2 ($p=0.000$). The patients with a mean of Tnewhepatic CI measurements less than 3 L/min/m2 received more colloid transfusion and had longer anesthesia time during OLT. There was a statistically significant relationship between cell-saver/kg use and hospitalisation ($p=0.008$), and an association between urine output and mortality ($p=0.024$). ***Conclusion:*** PiCCO monitoring provides flow and dynamic parameters which predict fluid responsiveness and make critical therapeutic decisions to restore hemodynamic stability in pediatric patients undergoing OLT.

Keywords: ***Invasive hemodynamic monitoring, liver transplantation anesthesia, cardiac output monitoring, pediatric liver transplant, pulse contour analysis***

Introduction

Orthotopic liver transplantation (OLT) is the gold standard in the treatment of end-stage liver disease (ESLD) in pediatric patients. Indications for OLT in children include; Extrahepatic cholestasis, intrahepatic cholestasis, metabolic disorders, acute liver failure, and primary liver malignancy [1]. Cirrhosis and portal hypertension are the most significant changes in these patients, which can be seen as abnormalities in the cardiovascular system: hyperdynamic circulation symptoms, increasing cardiac output (CO), decreasing systemic vascular resistance (SVR), and elevated MAP [2]. Hypovolemia, hemorrhage, major vessel manipulations, and reperfusion should be evaluated with cardiovascular monitoring [3]. Perioperative care, management, and hemodynamic monitoring of pediatric patients are very important. There are many CO measurement methods. Hemodynamic volumetric parameters monitored by the PiCCO system were MAP, CVP, CI, global end diastolic volume (GEDV), intrathoracic blood volume index (ITBVI), EVLWI, systemic vascular resistance index (SVRI) and SVV. All these additional variables can be helpful in decision making regarding hemodynamic stability [4,5].

The primary aim of this study was to demonstrate that PiCCO monitoring can be used to decide on fluid management early in the fluid monitoring process. The secondary aim was to analyze hemodynamic parameters in pediatric patients with OLT at baseline, anhepatic, and new hepatic phases.

Materials and Methods

This retrospective study was conducted with 41 consecutive patients aged between 4 and 204 months who underwent elective ESLD-OLT between September 2014 and October 2017. The research review board and each patient an authorized relative provided written consent to participate.

Retrospectively collected included demographic variables (age, weight, sex), pediatric end-stage liver disease (PELD) score, preoperative laboratory parameters, child classification, etiological causes, duration of anesthesia, length of stay in the intensive care unit (ICU), intraoperative data, hemodynamic and PiCCO values.

Anesthesia induction was performed in all patients using the same procedure and standard anesthetic monitoring (ECG, NIBP, $EtCO_2$, HR, SpO_2, Tº). Anesthesia was induced via the intravenous injection of 2-3 mg/kg propofol, 2 µ/kg fentanyl and 0.6 mg/kg rocuronium to facilitate endotracheal intubation. Anesthesia was maintained via the continuous infusion of 0.05-0.3 µ/kg/min remifentanil and 0.3 mg/kg/h rocuronium and inhaled sevoflurane at a concentration of 2-2.2%. Vasoactive and inotropic medications were started in case of hypotension after anesthesia induction. Norepinephrine infusion is especially helpful in cases of hypotension, low CO, and low SVR during postoperative LT or postreperfusion syndrome [6]. In these situations, we also used NE (0.01 to 0.5 /kg/min).

After induction of anesthesia, we used a method known as PiCCO, which is considered the gold standard for measuring CO in pediatric patients [7]. Under ultrasound guidance, an intravenous catheter (IVC) was inserted into the left or right jugular vein and an arterial catheter with a thermistor was inserted into the femoral artery (3-Fr PV2013L07 at <20 kg and 4-Fr PV2014L08 at >20 kg). A PiCCO device was used to connect the two catheters (version 5.2.2, Pulsion Medical Systems AG, Munich, Germany). A predetermined volume of cold saline was injected into the distal part of the IVC (5 mL at < 20 kg or 10 ml at >20 kg, at a temperature of <8°C). Measurements were performed at three-time points: Baseline ($T_{baseline}$), anhepatic phase ($T_{anhepatic}$), and reperfusion phase ($T_{newhepatic}$). These phases were defined as follows: $T_{baseline}$ as baseline 30 minutes after skin incision, $T_{anhepatic}$ as anhepatic phase after clamping the inferior vena cava, $T_{newhepatic}$ as new hepatic phase 30 minutes after reperfusion. The PiCCO system measures MAP (normal values 80-100 mmHg), SVRI (normal values 1200 to 2000 dynes. $sec.m^2.cm^5$), bolus thermodilution CI (normal values 3.5 to 5.0 $L.min^{-1}.m^2$), ITBVI (normal values 850 to 1000 mL/m^2), EVLWI (normal values 3.0 to 7.0 mL/kg), and SVV (normal values less than 10%).

Colloids and crystalloids were administered to maintain urine output at 0.5-1 ml/kg/h and CVP at 8 to 12 mm Hg, and ITBVI, CI, and SVV within normal limits. Intraoperative blood loss was compensated by transfusing packed red blood cells (RBCs) or whole blood to maintain optimal hemoglobin levels. Fresh frozen plasma (FFP) and platelets were administered based on age and laboratory findings. Platelets given when the count fell below $50x10^{9}$ /L, and FFP when the prothrombin time (PT) was longer than 20 seconds and also the international normalised ratio (INR). We planned the use of aprotinin, tranexamic acid, fibrinogen, and cryoprecipitate according to the patient's clinical and laboratory values (PT, INR, fibrinogen). The operations were performed by the same surgeons using the piggyback technique. Other methods of blood conservation used in our practice besides surgical technique were the use of cell saver, maintenance of low CVP, nitrate, diuretics, antifibrinolytics, fibrinogen, normothermia, patient positioning, and adequate ventilation.

Statistical Analysis

Statistical analyses were performed using the SPSS software package, version 22 for MAC (SPSS Inc., Chicago, IL). First, we ran the Shapiro Wilk test to evaluate normallity. Data were presented as mean ± SD. and (min.-max.). Student's t-test was used for the comparison of continuous variables when normally distributed and Mann–Whitney U test for skewed or non-normal distributed variables. Differences among categorical variables were tested with chi-square and Fisher's exact test, where appropriate. To compare, dependent variables, we used Friedman and Repeated Measures ANOVA tests according to assumptions. Correlations between scaler variables are defined by using Person/Spearman's rho and related p values. Any p-value less than 0.05 was considered statistically significant.

Results

The demographic variables collected for each patient were age, weight, sex, PELD score, preoperative laboratory parameters, child classification, etiological causes, duration of anesthesia, length of stay in the ICU, intraoperative data, hemodynamic and PiCCO values. Demographic outcomes: 41 (min 4 mo, max 17 yrs) patients who received a primary OLT from a living related donor were hemodynamically monitored during OLT with PiCCO. Therefore, we based our intraoperative clinical management in children on data obtained with PiCCO. 46.3% were female, 53.7% were male with an average body weight of 18.5 kg. The mean PELD score was 12.12±6.82 (2-25). Child classification: Child A 22.1%, Child B 57.1%, Child C 20.7% (**Table 1**). Percentage etiology of liver failure: 34.1 primary biliary causes, 17.1 fulminant, 9.8 progressive familial intrahepatic cholestasis, 7.3 urea cycle defect, 4.9 Wilson, 4.9 Crigler Najjar, 4.9 Hepatoblastoma, 2.4 Hyperoxalocis, 2.4 Cryptogenic, 2.4 Viral, 2.4 Hypercolestrolemia, 2.4 Otoimmune, 2.4 Budd Chiari, 2.4 Caroli congenital hepatic fibrosis (**Table 2**). The mean duration of anesthesia was 9.2±1.3 hours. The maximum lactate values were 6.7±3.95 (1.3-20). The portal clamp time was 70.2±12.08 (50-102). Intraoperative consumption of crystalloids 103.2±30.5 mL/kg, colloids 78.4±38.9 mL/kg, RBCs 27.3±30.0 mL/kg, FFP 5.6±10.2 mL/kg. The GRWR was 2.93±1.39 % (0.92-6.4). The length of stay in the ICU was 6.5±6.7 days. Hospitalization and mortality were not associated with demographic data, etiology, child classification, lenght of anesthesia, duration of the portal clemp, lactate maximum values, warm ischemia time, the use of crystalloid-colloid fluids and blood products, or length of stay in the ICU (**Table 1,2,3**). There was a statistically significant relationship between cell-saver/kg use and hospitalization (p=0.008), and an associations between urine output and mortality (p=0.024) (**Table 3**). Measurements including MAP, CVP and CI were significantly lower during the $T_{anhepatic}$ phase when compared to $T_{baseline}$ and $T_{newhepatic}$ phases ($p<0.05$ for all) (**Table 4**). Patients whose mean $T_{newhepatic}$ EVLWI was greater than 7 mL/kg had greater amounts of intraoperative blood transfused (p=0.027), higher GRWR (p=0.016), and longer anesthesia time (p=0.046). The mean value of $T_{newhepatic}$ SVV measurements was greater than 10% in patients with a higher GRWR (p=0.033). Patients with a GEDVI <650 mL/m^2 (p=0.000) required more blood transfusions and were observed to have a higher GRWR. Patients with mean $T_{newhepatic}$ CI measurements less than 3 $L/min/m^2$ received more colloid transfusions and had longer anesthesia time during OLT (**Table 5**).

Table 1: Patient demographics, PELD score, preoperative parameters and Child classification

Variables	Value (mean ± SD)
Age, months	60.8 ± 69.9 (4-204)
Weight, kg	18.5 ± 16.4
Sex (%) Male Female	 53.7 46.3
PELD score	12.12 ± 6.82 (2-25)
Preoperative Hemoglobin (g/dL)	 9.4 ± 1.0

Alanine aminotransferase (ALT)(U/L)	139.93 ± 364.96 (10-2332)
Aspartate aminoglutamate (AST)(U/L)	224.75 ± 472.02 (11-2883)
Total bilirubin (mg/dL)	9.67 ± 9.51 (0.1-27.8)
Direct bilirubin (mg/dL)	6.46 ± 6.77 (0.1 ± 20.9)
Albumin (g/dL)	3.19 ± 0.65 (1.7 ± 4.5)
Creatinine (mg/dL)	0.55 ± 0.43 (0.27 ±2.61)
International normalized ratio (INR)	1.5 ± 0.45 (0.91-2.85)
Child Classification (%)	
Child A	22.1
Child B	57.1
Child C	20.7

PELD: Pediatric End-Stage Liver Disease

Table 2. Etiological analysis (%)

Primary biliary causes (34.1)	Hyperoxalozis (2.4)
Fulminant (17.1)	Cryptogenic (2.4)
PFIC (9.8)	Viral (2.4)
Urea cycle defect (7.3)	Hypercolesterolemia (2.4)
Wilson (4.9)	Otoimmune (2.4)
Crigler Najjar (4.9)	Budd Chiari (2.4)
Hepatoblastoma (4.9)	Caroli congenital hepatic fibrosis (2.4)

PFIC: Progressive familial intrahepatic cholestasis

Table 3. Intraoperative and postoperative data

Duration of anesthesia (hours)	9.2 ± 1.3 (6.5-12.5)
Length of stay in the ICU (days)	6.5 ± 6.7
Intraoperative	
Cristalloids (mL/kg)	103.2 ± 30.5
Colloids (mL/kg)	78.4 ± 38.9
RBCs (mL/kg)	27.3 ± 30.0 (0-134)
FFP (mL/kg)	5.6 ± 10.2 (0-44.98)
Cell-saver (mL/kg)	20.09 ± 14.37 (0.02-53.85)
Urine output (mL/kg/h)	2.12 ± 1.68 (0.06-7.98)
Lactate max	6.77 ± 3.95 (1.3-20)
Portal clemp time	70.2 ± 12.08 (50-102)
Greft/recipient weight ratio (%)	2.93 ± 1.39 (0.92-6.4)

RBCs: Packed red blood cells
FFP: Fresh frosen plasma

Table 4. Patients' hemodynamic measurements and PiCCO parameters at $T_{baseline}$, $T_{anhepatic}$, $T_{newhepatic}$

	$T_{baseline}$	$T_{anhepatic}$	$T_{newhepatic}$
Mean arterial pressure (MAP)(mmHg)	59.3±11.0*	53.1±11.5**	57.0±10.1
Central venous pressure (CVP)(mmHg)	10.7±3.83•	9.03±4.01••	10.8±4.24
Cardiac index (CI) ($L/min^{-1}/m^2$)	5.3±2.27◘	5.2±4.23◘	7.4±3.07
Intrathoracic blood volume index (ITBVI) (mL/m^2)	524.0±173.9	523.5±113.8	640±315.3
Extravascular lung water index (EVLWI) (mL/kg)	14.5±9.89	13.5±7.63	10±12.7
Stroke volume variability (SVV) (%)	11.76±4.53	10.4±5.77	11.07±5.18
Systemic vascular resistance index (SVRI) dynes. $sec.m^2.cm^5$	954.0±404.2	887.3±509.5	998.4±590.8
Global end diastolic volume index (GEDVI)(mL/m^2)	638±329.7	63.8±307.9	646.6±216.1

* $p = 0.015$ compared with $T_{anhepatic,}$ ** $p = 0.008$ compared with $T_{newhepatic}$ value
• $p = 0.019$ $T_{baseline}$ compared with $T_{anhepatic,}$ •• $p = 0.021$ compared with $T_{newhepatic}$ value
◘ $p = 0.005$, ◘ ◘ $p = 0.021$ compared with $T_{newhepatic}$ value

Table 5. Statistical significance

$T_{newhepatic}$ EVLWI>7 mL/kg	
	Needed more blood transfusion (p=0.027)
	GRWR were bigger (p=0.016)
	Anesthesia time was longer (p=0.046)
$T_{newhepatic}$ SVV>10 %	
	Has larger GRWR (p=0.033)
$T_{newhepatic}$ GEDVI<650 mL/m^2	
	Needed more blood transfusion
	Corelation with GRWR (p=0.000)
$T_{newhepatic}$ CI<3 L/min/m2	
	Needed more colloid infusion
	Longer duration of anesthesia

Discussion

Detailed monitoring, adequate fluid replacement, and correct patient management are the most challenging tasks for anesthesiologist during OLT. It is important to give the appropriate amount and fluid to ensure adequate tissue perfusion and prevent multiple organ failures. On the other hand, the excessive cardiac filling may lead to pulmonary edema and hypoxemia [5]. We used PiCCO, a technique considered the gold standard for pediatric CO [7] measurement because of the importance of hemodynamic monitoring of pediatric patients during OLT.

Compared with intermittent TPTD, Geisen et al. [8] pointed out the limitations of the LiDCO, PiCCO, and FloTrac systems in obtaining accurate results in the postoperative period. We found that PiCCO conducted better in pediatrics OLT and offered the advantage of continuous real-time estimation.

In this study, hospitalization and mortality were not associated with demographic factors, etiology, child classification, lenght of anesthesia, length of the portal clemp, lactate maximum values, warm-ischemia time, the use of crystalloid-colloid fluids, or length of stay in the ICU (Table 1,2,3). We found a statistically significant association between cell-saver/kg use and hospitalization (p=0.008), as well as between urine output and mortality (p=0.024) (**Table 3**).

As a cross-comparison to PAC, PiCCO was also compared with LiDCO and FloTrac. The results showed that the values of PiCCO and LiDCO were equivalent within a clinically acceptable range [9]. ITBVI changes that occurred during the fluid loading had the highest area under the curve values and were statistically significant in identifying CI changes, regardless of the technique used to assess CI variation. To avoid mathematical coupling of PiCCO-derived parameters, Donati et al. [10] preferred to compare LiDCO-CI with ITBV. They reported little bias in CI values obtained with a radial artery LiDCO catheter and a femoral artery PiCCO catheter but less reliable precision. However, radial and femoral artery-derived SVV and PPV did not agree well [11]. ITBVI was more closely related to CI changes and better represented CI variations, whereas radial artery preload measurements were less closely related to CI and did not reflect CI changes. According to their previous studies, ITBVI was the best parameter for fluid response [12]. In our study, no significant difference was found for ITBVI between phases (**Table 4**).

Using CVP or SVV as a target parameter for the assessment of circulating blood volume, we evaluated hemodynamic parameters before and after reperfusion in children who participated in LT during anesthesia. When SVV is between 8% and 10%, improvement in hemodynamics with fluid administration has been reported [13]. The findings of Rudnick et al. [14] suggest that SVV may be a useful target parameter for intraoperative fluid management during OLT in children, although this has not been previously reported in pediatric patients. Measured values, including MAP, CVP and CI, were significantly lower during the $T_{anhepatic}$ phase than during the $T_{baseline}$ and $T_{newhepatic}$ phases ($p<0.05$ for all, Table 4). We found that the mean value of $T_{newhepatic}$ SVV measurements was greater than 10% in patients who had a higher GRWR (p=0.033). We also evaluated the comparison of the parameters we measured with PiCCO in OLT according to the phases and their relationships with fluid management. We found that the patients with mean $T_{newhepatic}$ CI measurements less than 3 L/min/m^2 received more colloid transfusions and had longer anesthesia time during OLT. Among the patients, more blood transfusions were needed and higher GRWR was observed in patients with GEDVI <650 mL/m^2 (p=0.000) (**Table 5**).

On the other hand, in our study, patients with a mean $T_{newhepatic}$ EVLWI greater than 7 mL/kg had greater amounts of intraoperative transfused blood (p=0.027), higher GRWR (p=0.016), and longer anesthesia time (p=0.046) (**Table 5**).

Although no one device is ideal, there are a variety of non-invasive methods to determine CO in a variety of patients and conditions (transesophageal echocardiography, pulse contour analysis, lithium dilution). The main function of these devices is to determine the patient's response to fluid administration in order to optimize resuscitation. It is important to emphasize that there is little evidence that any of these monitoring devices improve patient outcomes. PiCCO takes the lead even more. In addition, clinicians should incorporate the patient's clinical, hemodynamic, laboratory, and radiologic data to chart a course based on integrating and correctly interpreting these data rather than blindly following algorithms and bundles [14].

The rapid volume shifts and release of vasoactive mediators are seen intraoperatively, particularly stress and failure. More comprehensive values of blood volume, SVR, pulmonary vascular resistance, right ventricular afterload, and cardiac function can be obtained using PiCCO hemodynamic monitoring in patients with severe shock to guide fluid resuscitation and selection of vasopressor and inotropic medications such as NE and milrinone [15]. In such cases, we use NE and milrinone as vasopressor and inotropic medications.

The ideal hemodynamic monitor would be noninvasive, precise, and accurate and would provide continuous data during the transplantation process. Until this device is available, effective intraoperative care requires a comprehensive understanding of the applicability and limitations of current Technologies [5]. The minimal invasiveness of such systems, which is a particular advantage in the operating room, appears to be offset by lower reliability than more invasive devices [5].

Torgay et al. preliminarily reported on the parameters they monitored intraoperatively in pediatric patients undergoing OLT using the PiCCO. With their results, they interpreted the PiCCO system as a continuous, safe, multiparameter delivery method in pediatric OLT follow-up, and we determined that PiCCO could be safe and beneficial in pediatric patients by conducting a broader search based on this study [16].

Conclusion

PiCCO monitoring of EVLWI, SVV, and GEDVI is of major importance in predicting the fluid response of the pediatric patient undergoing OLT and determining early hemodynamic stabilization. We think that more PiCCO studies are needed in pediatric OLT patients to support our results in the future.

Acknowledgement

The abstract was presented as an oral presentation at The Transplantation Society 2018.

Conflict of Interest Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding source

The opinions delivered in this manuscript are our own, but not official positions of any organization or investor.

Ethical Statement

Institutional approval was obtained in advance of article submission from Baskent University Institutional Review Board (Project No: KA22/75).

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