European Journal of Therapeutics

DOI: 10.5152/EurJTher.2019.18020

Original Research

Comparison of Pulmonary Artery Catheter and Central Venous Catheter for Early Goal Directed Targeted Therapy in Sepsis and Septic Shock

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ABSTRACT

Objective: The aim of the present study was to compare the effect of the pulmonary artery catheterization (PAC) method and the central venous catheterization (CVC) method on hemodynamic and inflammatory parameters in early goal-directed therapy (EGDT).

Methods: This was a randomized prospective study. Patients with sepsis and septic shock within 12 h of diagnosis were included in the study. Each group received strict protocolized resuscitation for 72 h.

Results: The mean age of the patients was 63.4±14.5 years. The study included 15 (52%) male and 14 (48%) female patients. The length of stay in the hospital and the duration of mechanical ventilation were similar between the two groups. The length of stay in the intensive care unit was shorter in the CVC group (p=0.025). High mobility group box 1 levels were lower at 72 h in the CVC group (p=0.026). In the early resuscitation period, it was found that in the CVC-directed therapy group, the urine output and the mean arterial blood pressure were higher, but vasoconstrictor need was lower (p<0.05).

Conclusion: In the early resuscitation period, CVC-directed therapy is more effective, and rapid correction of hemodynamic parameters results in shorter intensive care unit stay. PAC is not superior to CVC-guided therapy in the late period.

Keywords: Early goal directed therapy, sepsis, septic shock

INTRODUCTION

Sepsis is a common disease with a high mortality rate (1). Fundamentally, the treatment consists of the removal of the trigger and the prevention of the tissue hypoperfusion and organ dysfunction. Several minutes after endotoxin release, cytokines are released, and these play an important role in pathogenesis (2). Mortality is significantly decreased by fluid resuscitation and early antibiotic induction which are the major steps in early goal-directed therapy (EGDT) (3).

Fluid resuscitation in EGDT is based on the central venous pressure (CVP) and central venous oxygen saturation ($ScVO_2$) measurements. In the early hemodynamic stage, vital signs, CVP (4), and urinary output (5) cannot detect global tissue hypoxia. A more definitive method to show the balance between systemic oxygen delivery and oxygen demand is the manipulation of preload, afterload, and contractility (6). Pulmonary artery (PA) catheter can be used to measure stroke volume, cardiac output (CO), mixed venous oxygen saturation (SvO_2), and intracardiac pressures to guide diagnosis and treatment (7).

The aim of the present study was to evaluate PA effectiveness in EGDT in a protocol-based study. For this reason, we used two different EGDT protocols based on two different catheterization methods in sepsis and septic shock to compare their effectiveness on hemodynamic goals and inflammatory parameters. The Protocolized Care for Early Septic Shock (PROCESS), Australasian Resuscitation in Sepsis Evaluation, and Protocolized Management in Sepsis trials show that EGDT has no mortality benefit compared with usual care (8-11). Our study was planned before these trials.

METHODS

This prospective randomized study was conducted in Erciyes University School of Medicine, Medical Intensive Care Unit (MICU) be-

How to cite: Elay G, Coşkun R, Gündoğan K, Güven M, Sungur M. Comparison of Pulmonary Artery Catheter and Central Venous Catheter for Early Goal Directed Targeted Therapy in Sepsis and Septic Shock. Eur J Ther 2019; 25(4): 253–8.

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Received: 03.09.2018 • **Accepted:** 13.05.2019

tween August 2010 and January 2012. Our study was approved by the ethics committee of Erciyes University School of Medicine (date: 08/07/2010; ethics committee decision no: 2010/61).

All patients or their families were informed about the study. For conscious patients, information was directly given to the patients, and for unconscious patients, families were informed. Written informed consent was obtained from the patients or their legally authorized representatives.

Inclusion Criteria

- Patients with severe sepsis and septic shock as defined according to the Surviving Sepsis Guidelines (12)
- Patients who were aged >18 years.

Exclusion Criteria

- Chronic liver disease
- Chronic renal failure
- Renal replacement therapy
- Pregnant
- Expected to die within 48 h
- Referred from another health care institution while they were being hospitalized there
- Patients who were aged <18 years
- Severe sepsis or septic shock diagnosis delayed more than 12 h
- Patients with chronic liver disease and chronic renal failure since they can affect lactate level.

The primary end points in our study were mortality and hemodynamic goals. A total of 29 patients were enrolled in the study. Baseline demographics, admission Glasgow Coma Scale, Acute Physiology Age Chronic Health Evaluation (APACHE II) score, daily Sepsis-Related Organ Failure Assessment score, arterial blood gas, arterial lactate levels, hourly urine output, vasopressor dose, length of hospital stay, length of intensive care unit (ICU) stay, duration of mechanical ventilation (MV), and 28-day mortality rate were recorded. Clinical data were collected at baseline; at 3, 6, 12, and 24 h; and on days 2 and 3. In addition, blood high mobility group box 1 (HMGB1) levels were measured at 20 and 72 h. Dopamine and noradrenaline were the initial choices as vasoconstrictor agents. Adrenaline was used in addition to dopamine or noradrenaline. During catheterization and measurements, midazolam (Dormicum®) and/or vecuronium (Norcuron®) were used for sedation and neuromuscular blockade, respectively.

Patients were randomly divided into the pulmonary artery catheterization (PAC) group (13, 14) and central venous catheterization (CVC) group. PA was used in the PAC group, whereas a CV catheter was used in the CVC group.

The patients were enrolled in the study within 12 h of severe sepsis or septic shock diagnosis. In each group, their own protocol was applied for at least 72 h.

PAC Group

In the PAC group, PA was inserted, and the protocol published by Pinsky and Vincent was used (15). For CO measurements, the thermodilution technique and a Vigilance CEDV (Edwards Lifesciences Corp., Irvine, CA, USA) device were used (15).

CVC Group

The protocol published by Rivers et al. in 2001 was used in the CVC group (13). To measure $ScVO_2$, blood extracted from the central catheter was immediately analyzed by a Siemens Rapidlab 1265, blood gas analysis device.

Statistical Analysis

The analysis was conducted using R 3.0.2 (www.r-project.org). Shapiro-Wilk test, histogram, and q-q plots were used to assess the normality of data. Levene's test was used to test variance heterogeneity. To compare the differences between the groups, a two-sided independent samples t test and Mann-Whitney U test were performed. In addition, one-way repeated measures analysis of variance and Friedman tests were used for time comparisons. A P value <5% was considered as statistically significant.

RESULTS

The mean age of the patients enrolled in the study was 63.4±14.5 years. A total of 29 patients were recruited into the study. There were 15 (52%) male and 14 (48%) female patients in the study (Table 1).

Table 1. Baseline demographic and clinical characteristics

Variables	CVC (n=15)	PAC (n=14)	p
Age (year) (±SD)	62±12	64±16	0.690
Male, n (%)	7 (46.7)	8 (57.1)	0.424
Underlying disease			
DM, n (%)	4 (26)	3 (21)	0.742
COPD, n (%)	1 (6.7)	4 (28)	0.119
CRF, n (%)	1 (6.7)	1 (7.1)	0.960
Malignancy, n (%)	3 (20)	1 (7.1)	0.316
CHF, n (%)	2 (13)	5 (35.7)	0.159
PVD, n (%)	2 (13)	2 (14.3)	0.941
SAH, n (%)	2 (13)	2 (14.3)	0.941
CVD, n (%)	2 (13)	1 (7.1)	0.584
pH (±SD)	7.34±0.1	7.30±0.1	0.278
Lactate (mmol/L) (±SD)	3.78±2.5	3.41±1.6	0.641
SOFA score day 1 (±SD)	7±3	9±2	0.141
SOFA score day 3 (±SD)	6±3	8±3	0.244
No. of organ failures	2 (13.3%)	4 (28.6%)	0.442

CVC: central venous catheterization; PAC: pulmonary artery catheterization; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CHF: chronic heart failure; PVD: peripheral vascular disease; SAH: systemic artery hypertension; CVD: cerebrovascular disease

Table 2. Effects of early goal–directed therapy protocols on hemodynamic parameters in the early phase of treatment

Variables	CVC (n=15)	PAC (n=14)	p
Median fluid amount (mL/h) (min/max)			
1 h	150.0 (50.0–600.0)	112.0 (50.0–1000.0)	0.228
2 h	100.0 (50.0–200.0)	100.0 (50.0–500.0)	0.854
3 h	100.0 (50.0–500.0)	100.0 (50.0–1000.0)	0.323
4 h	100.0 (50.0–200.0)	100.0 (50.0–260.0)	0.081
5 h	100.0 (50.0–200.0)	100.0 (50.0–260.0)	0.056
6 h	100.0 (50.0–200.0)	112.5 (50.0–260.0)	0.094
Median urine (mL/h) (min/max)			
1 h	0.00 (0.00–50.00)	0.00 (0.00–486)	0.782
2 h	0.00 (0.00–50.00)	5.00 (0.00–150.0)	0.706
3 h	40.00 (0.00–100.0)	10.00 (0.00–150.0)	0.116
4 h	20.00 (0.00–100.0)	10.00 (0.00–1 00.0)	0.138
5 h	50.00 (0.00–200.0)	5.00 (0.00–75.0)	0.028*
6 h	50.00 (0.00–250.0)	0.00 (0.00–100.0)	0.005
Vasoconstrictor need (µg/kg/min) (min–max)			
3 h	0.00 (0.00–0.50)	2.65 (0.00–20.0)	0.001
6 h	0.00 (0.00–0.25)	2.75 (0.00–20.0)	0.001
Cumulative fluid (mL/h) (min/max)			
Day 1	1395.0 (0.00–6729.0)	2972.0 (1278.0–9469.0)	0.023
Day 2	2167.0 (0.00–8965.0)	3285.0 (800.0–8004.0)	0.097
Day 3	2145.0 (0.00–5760.0)	2365.0 (0.00–5000.0)	0.678
Lactate (mmol/L) (±SD)			
3 h	2.85±2.46	3.29±1.70	0.579
6 h	2.54±1.62	3.20±1.66	0.292
MAP			
1 h	78.6±19.2	76.2±14.9	0.722
2 h	72.13±14.92	74.4±11.1	0.645
3 h	76.06±11.6	72.7±16.4	0.529
4 h	76.0±11.5	69.1±8.88	0.083
5 h	76.9±10.1	69.7±6.90	0.037
6 h	77.2±9.5	71.2±10.0	0.109
CVP (mmHg)			
3 h	8.66±4.04		
6 h	9.93±3.63		
PCWP (mmHg)			
3 h		15.50±4.25	
6 h		16.78±4.37	
$SCVO_2$ (±SD)			
3 h	67.0000±8.23		
6 h	67.4286±7.27		
SVO_2 (±SD)			
3 h		73.214±8.1	
6 h		74.571±7.9	

CVC: central venous catheterization; PAC: pulmonary artery catheterization; CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; $SCVO_2$: central venous oxygen saturation; SVO_2: mixed venous oxygen saturation

*<0.05

In the early phase (within 6 h), the patients in the PAC group had significantly higher vasoconstrictor needs (p=0.014) at 3 and 6 h (Table 2). The mean arterial pressure (MAP) (P<0.05) and urine output (p<0.05) were lower at only 5 h in the PAC group. The other clinical parameters were similar between both groups in the early phase. The length of stay in the hospital, the duration of MV, and 28-day mortality were similar between the two groups. In the CVC group, the length of stay in the ICU was shorter (p=0.025). In the CVC group, 24 h after the resuscitation period, lactate levels were lower. We did not observe any PAC-related complications. HMGB1 levels were lower at 72 h in the CVC group (p=0.026).

Table 3. Effects of early goal–directed therapy protocols on hemodynamic parameters in the late phase of treatment

Variables	CVC (n=15)	PAC (n=14)	p
Median urine (mL/day) (min/max)			
Day 2	1030 (50–6500)	2055 (200–3600)	0.158
Day 3	1330 (240–4900)	1972 (400–8400)	0.051
Median fluid amount (mL/day) (min/max)			
Day 2	4430 (1752–10,096)	4368 (300–9550)	0.880
Day 3	4300 (1791–6907)	4005 (1500–8110)	0.938
Noradrenaline dose (µg/kg/min) (min/max)	0.000 (0.0–0.1)	0.000 (0.0–1.5)	0.172
Dopamine dose (µg/kg/min) (min/max)	0.000 (0.0–20)	0.000 (0.0–20)	0.533
MAP (mmHg)			
12 h	84.6±15.7	68.7±11.2	0.005
24 h	92.8±16.5	66.6±15.6	0.000
Lactate (mmol/L) (±SD)			
12 h	1.80 (1.20–2.10)	2.52 (1.7–3.0)	0.102
24 h	1.6 (1.08–1.72)	2.64 (1.5–3.0)	0.029*
HMGB1, 20 h (ng/mL)	4.59±5.2	5.4±2.8	0.594
HMGB1, 72 h (ng/mL)	1.44±1.1	2.6±1.6	0.026*
Duration of MV (day) (min–max)	4 (1–65)	6 (1–24)	0.554
Length of stay in the ICU (day) (min–max)	5 (4–65)	14 (4–45)	0.025*
Length of stay in the hospital (day) (min–max)	6 (4–87)	19 (4–135)	0.058
Mortality, n (%)	8 (53%)	6 (43%)	0.424

CVC: central venous catheterization; PAC: pulmonary artery catheterization; MV: mechanical ventilation; MAP: mean arterial pressure; ICU: intensive care unit
*: $p<0.05$

Table 4. Culture isolates

	CVC	PAC	p
C. albicans, n (%)	3 (20)	1 (7)	0.316
A. baumannii, n (%)	3 (20)	6 (43)	0.184
S. maltophilia, n (%)	0 (0)	1 (7)	0.292
E. coli, n (%)	2 (13)	5 (35)	0.159
C. pneumoniae, n (%)	1 (6)	0 (0)	0.326

CVC: central venous catheterization; PAC: pulmonary artery catheterization

The patients were followed up for 72 h in the late phase; there was no difference with respect to daily urine amount, amount of fluid, and vasoconstrictor needs between the two groups (Table 3). Nine (60%) patients in the CVC group and 9 (64%) patients in the PAC group had positive culture results (Table 4).

DISCUSSION

In this single-center randomized study, we found that there was no difference between the treatment methods using PAC-directed therapy and CVC-directed therapy. In the CVC group, the length of stay in the ICU was shorter. Vasoconstrictor requirements were lower in the CVC group in the initial resuscitation period. Lactate levels were lower 24 h after the resuscitation period. The study protocol proposed by Pinsky and Vincent (15) was used in the PAC group, and the protocol proposed by Rivers et al. (13) was used in the CVC group. Our study was conducted in 2010; for this reason, the 2008 international sepsis guidelines were used as basis. The 2012 and 2016 international sepsis guidelines also have similar suggestion for hemodynamic goals with 2008 (11). The most important thing in management is early fluid resuscitation and infection control.

There are multiple studies about PA use in critically ill patients in specific and mixed patient populations with both positive and negative results (14, 16).

Although we had a very small patient group, our study can answer important questions since we used a specific homogenous

patient group. In 2001, Rivers et al. (13) reported that 28-day mortality decreases by 16% in the EGDT group. The major advantage of PA-directed therapies is that they can provide information about hemodynamic data which cannot be detected by clinical signs and CVC (17).

If PA data are interpreted correctly, they can detect intravascular volume in hypotensive patients, differentiate shock type, and monitor tissue oxygenation with SvO_2 levels. Despite all these beneficial effects, PA is expensive, experienced staff are needed for catheterization, and most physicians believe that usage can increase mortality. Therefore, these negative studies resulted in a significant decrease in PA use in critically ill patients (18). The first major study published in 1996 by Connors et al. (18) called the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) study showed increased 30-day mortality, length of ICU stay, and cost with PA use. In the SUPPORT study, the PAC group patients had a higher APACHE II score, lower MAP, and lower serum albumin levels than the other group, which may suggest that further studies need to be conducted (18). Other studies which criticize PA use concluded that PA use did not provide any beneficial effects. However, in all these studies, no particular protocols were used for PA use (16, 19-21).

In our study, the CVC group had a shorter ICU stay, meaning that effective early resuscitation results in more ICU-free days.

In the PROCESS study, there was no difference between the EGDT group and the usual care group with respect to early resuscitation and 60-day mortality rates. The study seriously questioned whether CVC-directed therapy is an indispensable method for sepsis and septic shock treatment (9). This landmark study is published in 2014. The results of the study indicate that awareness of sepsis is increased until this year and can be managed with fewer devices.

We did not observe any PA-related complications in our study, probably because of having only a small number of patients. The same person collected all of the data, the physician initiative was not taken into account, protocols were strictly applied to each group, the patient group was not changed, and the protocol was implemented until the end of the study.

Baseline positive end-expiratory pressure and PaO_2/FiO_2 values were different between the two groups. Although the envelope method was used, patients in the PAC group had more severe respiratory failure than those in the CVC group. This difference can be due to the small patient number. However, similar APACHE II scores in both groups show that there was no bias in selection of the patient. In the early stage, urine output and MAP were lower, and vasoconstrictor need was higher in the PAC group, indicating that early hemodynamic goals were not reached.

In contrast to the acute phase, in the late phase, there were no significant differences with respect to hemodynamic parameters, MV day, or 28-day mortality between the two treatment methods. This means that PAC-directed therapy is not superior to CVC-directed therapy. The length of stay in the ICU was shorter in the CVC-directed therapy group, meaning that effective early resuscitation results in more ICU-free days.

Since the study was conducted in a medical ICU, most of the patients had comorbidities. In the CVC group, the major co-morbidity was diabetes mellitus (26%). Patients with diabetes mellitus have a higher risk of infection (22). In the PAC group, the major co-morbidity was congestive heart failure, which also has infection risk.

Gram negative infections were associated with an increased risk of mortality in several studies (22). *Acinetobacter baumannii* was isolated in 13 (20%) patients in the CVC group, whereas it was 6 (43%) patients in the PAC group. We thought that the increased ratio of *A. baumannii* in the PAC group was due to longer ICU stay, but it had no effect on mortality rate.

Although there are many studies comparing the efficiency of the PAC and CVC methods, until now, no study has measured cytokine levels as well. Cytokines, such as tumor necrosis factor alpha, interleukin (IL)-1, IL-6, and HMGB1, have been shown to play an important role in organ dysfunction and cardiovascular disorders in sepsis and septic shock (23). No single biomarker showed sensitivity and specificity >90% for the diagnosis of sepsis or the prediction of outcome (24).

High mobility group box 1 is a late mediator released from macrophages 20 h after activation and remains at the plateau level for 72 h, so it can be detected within 20-72 h at the beginning of sepsis (24). Since it can be detected in serum for a long time, we preferred HMGB1 as a cytokine in our study. HMGB1 levels were low in both groups at 20 h, but at 72 h, the level was significantly lower in the CVC group, which may mean that the inflammatory process was less activated with CVC-directed therapy because of the faster recovery of hemodynamics in this group.

The study was conducted on a very small group of patients and in a single center. Catheters were replaced by only two physicians who had PAC insertion training. All those reasons affect the patient number and study result.

Since the study was conducted in a medical ICU, the results cannot be generalized to other ICUs, such as surgical ICU and mix ICU.

We did not accept all patients. We excluded moribund patients since the protocol should be applied for 72 h.

CONCLUSION

In the early resuscitation period, CVC-directed therapy is more effective on hemodynamic parameters. In the late period, PAC is not superior to CVC-guided therapy. PA is expensive, insertion is a complex process, and it needs special training. For all those reasons, we do not recommend PAC use for hemodynamic monitoring in sepsis and septic shock in medical ICU patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University (date: 08/07/2010; decision no: 2010/61).

Informed Consent: Written informed consent was obtained from patients and authorized representatives who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S., M.G.; Design - R.C., M.S.; Supervision - G.E., M.G.; Resources - G.E.; Data Collection and/or Processing - G.E., R.C.; Analysis and/or Interpretation - G.E., K.G.; Literature Search - G.E., M.S.; Writing Manuscript - G.E., R.C., K.G.; Critical Review - K.G., M.G.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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