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

Running head: Early Goal Directed Targeted Therapy in Sepsis

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Abstract

Objective: The aim of this 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 is a randomized prospective study. Patients with sepsis and septic shock within 12 hours of diagnosis were included in the study. Each group received strict protocolized resuscitation for 72 hours.

Results: The mean age of the patients was 63.4 ± 14.5 years. The study included 15 males (52%) and 14 females (48%).
The length of stay in hospital and the duration of mechanical ventilation (MV) were similar between the two groups. The length of stay in the intensive care unit was shorter (P = 0.025) in the CVC group. High mobility group box- 1(HMGB-1) levels were lower at 72 hours 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 ICU stay. PAC is not superior to CVC guided therapy in the late period.

Keywords: Sepsis, Early goal directed therapy, 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 endotoxine release, cytokines are released and these have 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 catheter (PA) can be used to measure stroke volume, cardiac (CO) output, mixed venous oxygen saturation (SvO_2) and intracardiac pressures to guide diagnosis and treatment (7).

Our aim 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 PROCESS (Protocolized Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis

Evaluation), and PROMISE (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.

Patients and Methods:

This prospective randomized study was conducted in University Faculty of Medicine, Medical Intensive Care Unit (MICU) between August 2010 and January 2012. Our study was approved by the Ethics Committee of University Faculty of Medicine (date: 08.07.2010; Ethics Committee decision number: 2010/61).

All patients or their families were informed about the study. For conscious patients, information was directly given to the patients, for unconscious patients, families were informed. The patients or their legally authorized representatives provided written informed consent.

Inclusıon criteria:

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

Exclusion criteria:

Chronic liver disease

Chronic renal failure,

Renal replacement therapy

Pregnant

Expected to die within 48 hours

Referred from another health care institution while they were being hospitalized there Younger than 18 years old

Severe sepsis or septic shock diagnosis delayed more than 12 hours . We exclude patients with chronic liver disease and chronic renal failure since they can affect lactate level.

Primary end points in our study were mortality and hemodynamic goals. 29 patients were enrolled in the study. Baseline demographics, admission Glasgow Coma Score (GCS), Acute Physiology Age

Chronic Health Evaluation (APACHE II) Score, daily Sepsis-Related Organ Failure Assessment (SOFA) 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 the 3rd, 6th, 12th and 24th hours, and on the 2nd and 3rd days. In addition, blood HMGB-1 levels were measured at the 20th and 72nd hours. Dopamine and noradrenaline was the initial choices as a vasoconstrictor agent. Adrenaline was used in addition to dopamine or noradrenaline. During the catheterization and measurements, midazolam (Dormicum)® and/or vecuronium (Norcuron)® were used for sedation and neuromuscular blockade respectively.

Patients were randomly divided into PAC group (15) and CVC group (14) and for the randomization, envelope method was used (25). PA was used in the PAC group while a central venous (CV) catheter was used in the CVC group.

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

Pulmonary artery catheter group:

In the PAC group, PA was inserted and the protocol published by Pinsky and Vincent was used (13). For CO measurements, the thermodilution technique, a Vigilance CEDV (Edwards Lifesciences Corp.Irvine, CA USA) device was used (13).

Central venous catheter group:

The protocol published by Rivers and colleagues in 2001 was used in the CVC group (14). To measure $ScVO_2$, blood taken from the central catheter was immediately analyzed with a Siemens Rapidlab 1265, blood gas analysis device.

Statistical Analysis:

The Shapiro-Wilk's test was used; also histogram and q-q plots were examined to assess the data normality. The Levene's test was used to test variance heterogeneity.

To compare the differences between groups, a two-sided independent samples t test and Mann-Whitney U test were performed. Also, one-way repeated measures analysis of variance and Friedman tests were used for time comparisons. The analysis was conducted using R 3.0.2 (www.r-project.org). A P value less than 5% was considered as statistically significant.

Results:

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

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

The patients were followed for 72 hours, in the late phase; there was no difference in terms of daily urine amount, amount of fluid andvasoconstrictor needs between the two groups (Table 3). In the CVC group 9 (60%) and in the PAC group 9(64%), patients 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 by the PAC- directed therapy and CVC-directed therapy. In the CVC group, the length of stay in ICU was shorter. Vasoconstrictor requirements were lower in the CVC group in the initial resuscitation period. Lactate levels were lower 24 hours after the resuscitation period. The study protocol proposed by Pinsky and Vincent used inthe PAC group and protocol proposed by Rivers and colleagues was used in CVC group (13, 14). Our study was conducted in 2010, for this

reason 2008 international sepsis guidelines taken as base. 2012 and 2016 international sepsis quidelines also have similer 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 (15, 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 the Rivers and colleagues was reported that 28-day mortality fell by 16% in the early goal directed therapy group (14). The major advantage of PA directed therapies is that, they can provide information about hemodynamic data which can not 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 can monitor tissue oxygenation with mixed venous oxygen saturation levels. Despite all these beneficial effects, PA is expensive, experienced staff are needed for catheterization and most physicians believe that usage can increase mortality. Consequently, 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 and colleagues and called the SUPPORT (Study to Understand Prognoses and Preferences for Outcomesand Risksof Treatments) 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 mean arterial pressure and lower serum albumin levels than the other group which may suggest that further studies need to be done (18). Other studies which criticize PA use concluded that PA use did not provide any benefical 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 in terms of 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. Results of the study indicates that awareness of sepsis is increased until this year and can be managed with less device.

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 and 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 PEEP and PaO2/FiO2 values were different between the two groups.Although the envelope method was used patients in the PAC group had more severe respiratory failure compared to the CVC group. This difference can be due to small patient number. However, similar APACHE II scores in both groups shows that there was no bias in selection of the patientIn 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 reachedA

In contrast to the acute phase, in the late phase, there were no significant differences in terms of 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 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, major co-morbidity was diabetes mellitus (26%). The 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 have infection risk.

Gram negative infections were associated with an increased risk of mortality in several studies (22). A.*baumannii* was isolated i3 (20%) patients in CVC group while 6 (43%) patientsin 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 TNF-α, IL-1, IL-6, and high-mobility group box 1 (HMGB1), have been shown to have an important role in organ dysfunction and cardiovascular disorders in sepsis and septic shock (23). No single biomarker showed sensitivity and specificity greater than 90% for the diagnosis of sepsis or the prediction of outcome (24).

HMGB1 is a late mediator released from macrophages 20 hours after activation and remains at the plateau level for 72 hours, so it can be detected within 20- 72 hours at the beginning of the 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 the 20^{th} hours, but at the 72^{nd} hours 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.

Limitations of the study:

Studywas conducted with a very small group of patients and in an single center. Catheters were replaced by only 2 physicans who had PAC insertion training. All those reasons affect the patient number and study result.

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

We didn't take all patients, we exclude moribound patients since the protocol should be applied 72 hours

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

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Table1: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
Number of organ failures	2(13.3 %)	4(28.6 %)	0.442

MAP:Mean arterial pressure, HR:Heart rate, RR:Respiratory rate, GCS:Glascow coma scale, DM:Diabetes mellitus ,CRF:Chronic renal failure,CHF:Chronic heart failure ,PVD Peripheral vascular disease, SAH:Systemic artery hypertension ,CVD:Cerebro vascular disease ,PEEP:Positive end expiratory pressure

TABLE-2: Effects of early goal-directed therapy protocols on hemodynamic parameters in early phase of treatment

Variables	CVC (n=15)	PAC (n=14)	P
Median fluid amount (mL/hour) (min./maks.)			
1hour	150.0 (50.0 - 600.0)	112.0 (50.0 - 1000.0)	0.228
2hours	100.0 (50.0 - 200.0)	100.0 (50.0 - 500.0)	0.854
3hours	100.0 (50.0 - 500.0)	100.0 (50.0 - 1000.0)	0.323
4hours	100.0 (50.0 - 200.0)	100.0 (50.0 - 260.0)	0.081
5hours	100.0 (50.0 - 200.0)	100.0 (50.0 - 260.0)	0.056
6hours	100.0 (50.0 - 200.0)	112.5 (50.0 - 260.0)	0.094
Median urine. (mL/hour) (min./maks.)			
1hour	0.00 (0.00 - 50.00)	0.00 (0.00 - 486)	0.782
2hours	0.00 (0.00 - 50.00)	5.00 (0.00 - 150.0)	0.706
3hours	40.00 (0.00 - 100.0)	10.00 (0.00 - 150.0)	0.116
4hours	20.00 (0.00 - 100.0)	10.00 (0.00 - 1 00.0)	0.138
5hours	50.00 (0.00 - 200.0)	5.00 (0.00 - 75.0)	**0.028**
6hours	50.00 (0.00 - 250.0)	0.00 (0.00 - 100.0)	0.005
Vasoconstrictor need(µg/kg/min) (min-max)			
3hours	0.00 (0.00 - 0.50)	2.65 (0.00 - 20.0)	**0.001**
6hours	0.00 (0.00 - 0.25)	2.75 (0.00 - 20.0)	**0.001**
Cumulative fluid(mL/hour) (min./maks.)			
1st day	1395.0 (0.00 - 6729.0)	2972.0 (1278.0 -	**0.023**
2nd day	2167.0 (0.00 - 8965.0)	9469.0)	0.097
3rd day	2145.0 (0.00 - 5760.0)	3285.0 (800.0- 8004.0)	0.678
		2365.0 (0.00- 5000.0)	
Lactate(mmol/L)(± SD)			
3hours	2.85 ± 2.46	3.29 ± 1.70	0.579
6hours	2.54 ± 1.62	3.20 ± 1.66	0.292
MAP	78.6 ± 19.2	76.2 ± 14.9	0.722
1hour	72.13 ± 14.92	74.4 ± 11.1	0.645
2hours	76.06 ± 11.6	72.7 ± 16.4	0.529
3hours	76.0 ± 11.5	69.1 ± 8.88	0.083
4hours	76.9 ± 10.1	69.7 ± 6.90	**0.037**
5hours	77.2 ± 9.5	71.2 ± 10.0	0.109
6hours			
Cvp(mmHg)			
3hours	8.66 ± 4.04		
6hours	9.93 ± 3.63		
Pcwp(mmHg)		15.50 ± 4.25	
3hours		16.78 ± 4.37	
6hours			
$SCVO_2$ (± SD)			
3.hours	67.0000 ± 8.23		
6.hours	67.4286 ± 7.27		
SVO2 (± SD)			
3.hours		73.214 ± 8.1	

6.hours	74.571 ± 7.9

CVP:Central venous pressure, PCWP:Pulmonary capillery wedge pressure

Table-3: Effects of early goal-directed therapy protocols on hemodynamic parameters in late phase of treatment

Variables	**CVC (n:15)**	**PAC (n:14)**	**P**
Median urine (day**/**mL)(min./maks.)			
2nd day	1030 (50 - 6500)	2055 (200 - 3600)	0.158
3rd day	1330 (240 - 4900)	1972 (400 - 8400)	0.051
Median fluid amount(mL/day)(min./maks.)			
2nd day	4430 (1752 - 10096)	4368 (300 - 9550)	0.880
3rd day	4300 (1791 - 6907)	4005 (1500 - 8110)	0.938
Noradrenalin Dose (µg/kg/min) (min./maks.)	0.000 (0.0 - 0.1)	0.000 (0.0 - 1.5)	0.172
Dopamin Dose (µg/kg/min)(min./maks.)	0.000 (0.0 - 20)	0.000 (0.0 - 20)	0.533
MAP(mmHg)			
12.hours	84.6 ± 15.7	68.7 ± 11.2	0.005
24.hours	92.8 ± 16.5	66.6 ± 15.6	**0.000**
Lactat(mmol/L) (± SD)			
12.hours	1.80 (1.20 - 2.10)	2.52(1.7 - 3.0)	0.102
24.hours	1.6 (1.08- 1.72)	2.64 (1.5 - 3.0)	**0.029***
HMGB1-20.hour (ng/mL)	4.59 ± 5.2	5.4 ± 2.8	0.594
HMGB1-72.hour (ng/mL)	1.44 ± 1.1	2.6 ± 1.6	**0.026***
Duration of MV	4 (1-65)	6 (1-24)	0.554

(Day) (min-max)			
Lenght of stay in ICU (Day) (min-max)	5 (4-65)	14 (4-45)	**0.025***
Lenght of stay in hospital (Day) (min-max)	6 (4-87)	19 (4-135)	0.058
Mortality, n(%)	8 (% 53)	6 (% 43)	0.424

MV:Mechanical ventilation,MAP:Mean arterial pressure,ICU:Intensive care unit

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