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ORIGINAL RESEARCH **INTENSIVE CARE**

The effect of fluid balance, norepinephrine and blood glucose levels on syndecan-1 level in sepsis patients

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Abstract

Background & objective. Damage to the endothelium glycocalyx layer can cause sepsis. Several diverse factors have been suggested to worsen the damage, such as high mean fluid balance, high norepinephrine doses, high blood glucose levels, and high baseline levels of syndecan-1 level. This study aimed to show that these components are risk factors for aggravated damage to the endothelium glycocalyx layer, as seen by syndecan-1 levels, and also to find the relation between norepinephrine dose and mortality in sepsis patient.

Methodology: This observational analytic study was conducted using a prospective, cohort approach on sepsis patients aged between 18 to 65 y, who were treated at our intensive care unit (ICU) from March 2021 to June 2021. A total of 40 subjects were assigned into two groups and monitored for three days. On day 0 and day 3, the levels of syndecan-1 were analyzed. Statistical test analysis used chi square and Mann Whitney tests, followed by a multivariate assessment using the logistic regression test to determine the significance with $P < 0.05$. The patients were followed till they were discharged from the hospital to determine the mortality rate.

Results: Mean fluid balance, mean norepinephrine dose and glucose level had no significant relation with syndecan-1 level ($P = 1$, $P = 0.145$, and $P = 1$, respectively). Meanwhile norepinephrine dose of more than 0.1 µg/kg/min was related significantly with death ($P = 0.016$).

Conclusion. In septic patients, fluid balance, norepinephrine dose and blood glucose do not associate with syndecan-1 level. However, norepinephrine dose relates to mortality significantly

Keywords. Sepsis, norepinephrine, fluid balance, hyperglycemia, glycocalyx, *syndecan*-1

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1. Introduction

Sepsis is potentially a fatal organ malfunction caused by the body's inability to fight infection. In recent decades, sepsis has been a cause for serious concern. In 2017, 48.9 million individuals were diagnosed with sepsis, with 11 million dying as a result. This means that one out of every four sepsis patients died. Damage to the endothelium glycocalyx (eGCX), is currently thought to

be the cause of organ failure, which leads to mortality in sepsis. The endothelial glycocalyx layer is a layer that is responsible for maintaining the endothelium's integrity. If this layer is damaged, the capillary endothelium will disintegrate, resulting in cell hypoperfusion.[1–8]

Damage to the eGCX can be induced not only by sepsis, but also by a variety of other factors. High mean fluid balance, blood glucose levels, use of norepinephrine in large doses, and the baseline syndecan-1 levels are among them. When the mean fluid balance is high, it stimulates the release of alpha-natriuretic peptide, resulting in direct damage to the eGCX. A high blood glucose level promotes the production of reactive oxygen species (ROS), which act as free radicals and destroys the eGCX directly. Examples of ROS include peroxides, superoxide, hydroxyl radical, singlet oxygen, and alpha-oxygen. In vitro studies have shown that high doses of norepinephrine trigger oxidative stress, which increases free radical level in the body, causing direct damage to the eGCX, which increases mortality in septic patients if the damage is severe.[9–18]

The eGCX can be damaged in a variety of ways, both directly and indirectly. The increase in syndecan-1 levels in the plasma is an indirect parameter to identify damage to the eGCX. Syndecan-1 is one of the components of the main eGCX, and it is very vulnerable to disruption. [19,20]

We investigated whether fluid balance, norepinephrine dose, and blood glucose level relate to syndecan-1 level in patient with sepsis, which could identify damage to eGCX. In addition, we also assessed the relation between norepinephrine dose and the mortality.

2. Methodology

A prospective cohort study with successive sampling technique was carried out in septic patients treated at Dr. Moewardi Hospital, Surakarta, Indonesia from July 2021 to October 2021. At the time of admission to the ICU, the patient's identification, medical record number, date of admission to the ICU, and the first diagnosis were documented. We also recorded weight, height, SOFA levels, consciousness level, vital signs, ventilator mode, use of vasopressor medicines, fluid balance, current blood glucose levels, and vasoactive inotropic score. Syndecan-1 levels were measured on the first and third days of treatment in the ICU. To determine the mortality rate, the subjects were observed throughout the course of their illness until they were discharged from the hospital. A statistical data processing program was used to process the data. The findings of the variables were displayed as frequency and percentage. Homogenization analysis between groups for confounding variables was done utilizing bivariate analysis and chi square analysis for the categorical variables. The P > 0.05 was considered significant. Reseinbles homogeniety multivariate

analysis was done utilizing logistic regression, using chi square analysis for categorical data and Mann Whitney analysis for numerical variables. The level of significance employed was 5%.

3. Results

Male gender dominated our study group 26 (59%) and their mean age was 53.4 ± 11.0 y (range 36.0 – 72.0 y). The females (41%) had the mean age 50.9 ± 12.2 y (range 29.0 – 72.0 y). There was no significant difference in term of mean age between males and females (P = 0.912). Overall mean age ranged from 51 to 53 y.

The proportion of syndecan-1 was defined as the percentage of the difference between the last syndecan-1 and the baseline syndecan-1 level. On the third day, if the proportion value of syndecan-1 level was positive, it referred to a rise in syndecan-1 level. Meanwhile the proportion value of syndecan-1 level was negative, the syndecan-1 decreased on the third day. When compared to the baseline syndecan-1 levels, the majority of subjects (81.8 %) demonstrated a drop in syndecan-1 level on the third day. Only 9.1% of subjects had a 30% increase in the last syndecan-1 level when compared to the baseline syndecan-1 levels.

Estimated mean baseline syndecan-1 levels in patients :

- Experiencing a 30% increase: 4.4 (1.6 – 7.1)
- No increase by 30%: 8.2 (7.8 – 8.6)

A lower baseline syndecan-1 level was associated with a 30% increase in syndecan-1 level.

Subjects whose syndecan-1 level increased more than 30% had lower mortality rate (25% vs. 75%) than those whose syndecan-1 level was 30% and below (50% vs. 50%). However, at a 5% level of significance, the difference in the proportion of death between these groups did not demonstrate a significant difference (P = 0.609).

The relation between norepinephrine dose and mortality in these subjects was statistically significant; e.g., 14 vs.

Table 1: Distribution of syndecan-1 (ng/ml) at day 0 and the third day

Parameter	Day Zero (ng/ml)	Day 3 (ng/ml)	Proportion %
Mean ± SD	7.83 ± 1.63	6.81 ± 1.71	-0.06 [0.49
Median	8.40	7.10	-0.14
Range	2.19 - 9.76	2.61 - 9.72	-0.7 - 2.37

Table 2: Distribution of blood glucose, fluid balance and norepinephrine dose

Distribution	Day 0	Day 1	Day 2	Day 3
Blood Glucose (mg/dL)				
Mean ± SD	211 ± 48	216 ± 37	212 ± 32	211 ± 28
Range	107 - 357	143 - 349	124 - 320	174 - 333
Fluid Balance (mL)				
Mean ± SD	1.183 ± 642	1.540 ± 647	1.860 ± 676	2.134 ± 742
Range	360 – 3.290	640 – 3.440	860 – 3.820	1.110 – 4.680
Norepinephrine dose (µg/kg/min)				
Mean ± SD	0.05 ± 0.05	0.05 ± 0.05	0.05 ± 0.06	0.06 ± 0.07
Range	0.00 – 0.15	0.00 – 0.15	0.00 – 0.15	0.00 – 0.20

Table 3: Distribution by increase in syndecan-1

Variable	> 30%		≤ 30%		p*
	Range	Mean ± SD	Range	Mean ± SD	
Blood Glucose (mg/dL)	175 - 357	227 ± 87	107 - 320	210 ± 44	0.922
Fluid Balance (mL)	560 - 1.640	940 ± 488	360 - 3.290	1.207 ± 655	0.373
Norepinephrine dose (µg/kg/min)	0.00 – 0.10	0.05 ± 0.06	0.00 – 0.15	0.05 ± 0.05	0.984

** Mann-Whitney test*

Table 4: Distribution of early and last syndecan-1 by group 30% increase syndecan-1

Measurement time		Syndecan-1	
		≤ 30%	> 30%
Early syndecan-1	Range	5.14 – 9.76	2.19 – 6.38
	Mean ± SD	8.18 ± 1.16	4.3618 ± 1.71
Last syndecan-1	Range	2.61 – 9.37	7.38 – 9.72
	Mean ± SD	6.6418 ± 1.69	8.4818 ± 0.98

7 (p = 0.016) at a dose of ≥ 0.1 µg/kg/min, with a relative risk rate of 2.1.

4. Discussion

There was no significant difference in the two age groups based on sex (P = 0.912), with the mean age range of 50.9 years in females (41%) and 53.4 years in male group (59%). We also discovered that the means syndecan-1 concentration were 7.83 ng/ml on the first day and 6.81 ng/ml on the third day. This is consistent with an earlier studyby Murphy et al. In individuals with sepsis due to a lung infection, the syndecan-1 levels were not excessively high and even tended to decrease. Heparin sulfate marker is better than syndecan-1 in defining glycocalyx endothelial damage in septic patients with pneumonia. Furthermore, Hatanaka et al. published in 2021 that the syndecan-1 levels of septic patients did not increase significantly from day 1 to day 3, but syndecan-1 at day 3 was a predictor of death on 28 days. But in patients whose syndecan-1 levels had been high since the first day, it did not increase significantly on the third day, even though the syndecan-1 levels were still high. The level of syndecan-1 on the first day, with a cut off of 17-25 ng/ml was also reported to have a substantial effect on the morbidity and death of septic patients.[21,22]

In our study from the first to the third day, the mean daily blood glucose level was > 200 mg/dl. Despite the fact that the daily mean value was relatively high, it had no effect on the increase in syndecan-1 levels. This is in line with study undertaken by Jaiswal et al. in 2020 and Warren Jr et al. in 2017, both of which found that lower levels of syndecan led to increased glucose intolerance, increased insulin resistance, and higher glucose levels.[23,24]

The mean levels of syndecan-1 was found to be rather low in our study, while the mean daily blood glucose level was relatively high. Patients whose syndecan-1

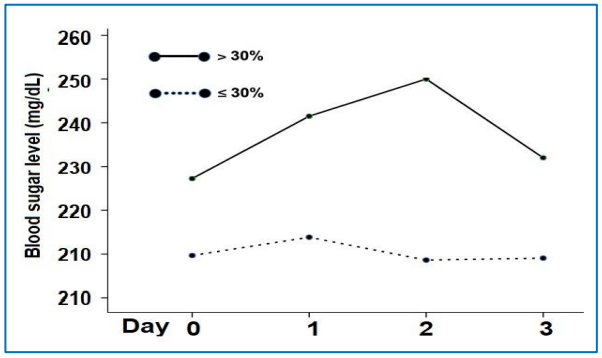

Figure 1: Changes in blood glucose level for three days based on a 30% increase in syndecan-1

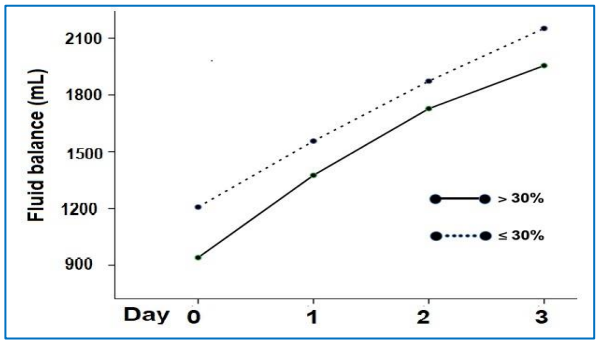

Figure 2: Changes in fluid balance for three days based on a 30% increase in syndecan-1

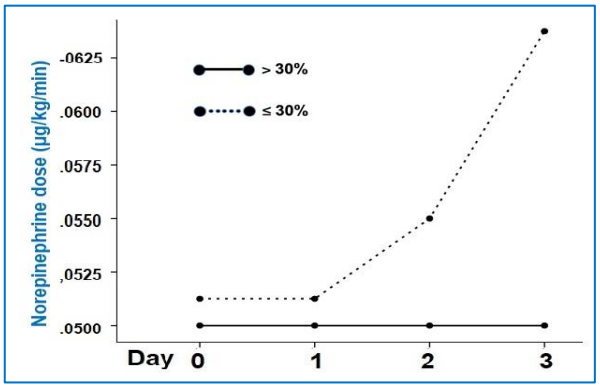

Figure 3: Norepinephrine dosage for three days based on a 30% increase in syndecan-1

levels increased by more than 30% had blood glucose levels above 220 mg/dl on a daily basis, whereas patients, whose syndecan-1 levels did not rise by more than 30%, had more stable blood glucose level of below 220 mg/dl on a daily basis, though this it was not statistically significant. Perhaps increased blood glucose level induces the elevation of syndecan-1 levels. This generates a vicious cycle in which low level of syndecan-1 causes an increase in blood glucose, while high blood glucose level causes more damage to the eGCX, which is characterized by elevated syndecan-1 level.

Our findings demonstrate that the mean daily cumulative fluid balance was 1183 ml on the first day and gradually enhanced reaching 2134 ml on the third day. A bivariate analysis of fluid balance >1500 ml versus a 30% increase in syndecan-1 levels, revealed that these two were not statistically significant (P = 1). Patients with a syndecan-1 level increase of more than 30% had a lower mean cumulative fluid balance of 940 ml, while patients with a syndecan-1 level increase of less than 30% had mean cumulative fluid balance of 1207 ml on the first day. This is similar to that found by Puskarich's 2016 study, showing that fluid delivery had no influence on syndecan-1 levels. Syndecan-1 levels increased in subjects receiving high amounts of fluids (> 4000 ml) and intubated, but did not increase in those given large amounts of fluids (> 4000 ml) but not intubated; or in those given small amounts of fluids (< 4000 ml). Similar results were obtained on syndecan-1 examination at 6 hours in another study by Saoraya (2021), which compared the administration of 35 ml/kg vs 53 ml/kg resuscitation fluids. The difference was not significant (P = 0.07). They found a dose of 35 ml/kg, or roughly 1750 ml at 50 kg, could lower syndecan-1 levels, An animal study by Xin Wu in 2017 showed that syndecan-1 levels were lower in septic mice given fluid resuscitation than in septic mice, which were not given fluid resuscitation. This suggests that large volumes of fluid alone are insufficient to damage the eGCX, characterized by an increase in syndecan-1; in fact, proper fluid resuscitation in septic patients can lower syndecan-1 levels, which is consistent with our findings. This is in line with the latest resuscitation guidelines from the surviving sepsis campaign, which recommend giving septic patients an initial fluid resuscitation of 30 ml/kg body weight. Syndecan-1 levels were actually lower in our subjects who received fluid equal to 30 ml/kg.[8,25,26]

Our finding that syndecan-1 level did not significantly relate to norepinephrine levels was consistent with Liang's study in 2021, in which norepinephrine was administered to patients undergoing major surgery, and syndecan-1 levels did not differ significantly between those receiving norepinephrine and not receiving norepinephrine at 6 hours. Similarly, in Saoraya's study (2021), no significant differences in syndecan-1 levels were identified between septic patients who got norepinephrine and those who did not.[26,27]

In our study, the mean syndecan-1 level decreased due to the possibility of vasoplegia in patients with sepsis, whereas in a study conducted by Abou-Arab (2019) in post-cardiac surgery patients who experienced vasoplegia, the level of syndecan-1 was lower than those who did not experience vasoplegia, and this is likely due to the fact that syndecan-1 has little to do with the mechanotransduction mechanism which triggers the release of NO, inducing vasoplegia in sepsis.[27,28]

A study conducted by Potje in 2021 found evidence that syndecan-1 was not directly associated to endogenous norepinephrine control in the body; perhaps this is why the levels of syndecan-1 in our study did not differ significantly across groups receiving different norepinephrine doses. The secondary outcome of our trial, and showed that norepinephrine dose levels of 0.1 µg/kg/min had a significant relation with mortality in septic patients. This is in line with the SOFA score, indicating that administering norepinephrine at a rate of 0.1 µg/kg/min increases the probability of critical patients dying.[28,29]

5. Limitations

There are various drawbacks to this study, including the fact that it was a cohort study, which allows for the occurrence of confounding factors that the researcher cannot control. Furthermore, the 0 point, which began when the patient was admitted to the tertiary ICU does not always reflect the 0 point of sepsis itself, and may skew the syndecan-1 data. In addition, several forms of infections, including pulmonary and non-pulmonary diseases, might cause syndecan-1 levels to be bias. Nonetheless, this study can be used as a preliminary one to guide future studies on glycocalyx in septic patients by other researchers.

6. Conclusion

Norepinephrine dose of 0.1 µg/kg/min is significantly related to mortality in septic patients, with a risk relative of 2.1. But the increase in syndecan-1 levels in septic patients was not substantially connected to the mean fluid balance level, the mean dose of norepinephrine used, or the blood glucose level. Overall syndecan-1 level below 90 ng/ml has no relation with mortality.

7. Conflict of interest

None declared by the authors.

8. Authors' contribution

All of the authors took part in the study as main researchers.

SA Permana is the main author of this manuscript.

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