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Original Article

Effect of soluble CD14 subtype on the prognosis evaluation of acute paraquat poisoning patients

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Abstract: Objective: To study the relationship between soluble CD14 subtype (also named presepsin) and the prognosis of acute paraquat poisoning (APP) patients. Methods: We studied 85 APP patients who were divided into three groups: light (21 cases), moderate (37 cases) and heavy poisoning (27 cases) groups. Fifty healthy subjects were as control group. According to the conditions of prognosis, they were divided into two groups: survive group (28 cases) and death group (57 cases). We measured the concentration of presepsin in serum and the levels of CRP, TNF-α, IL-6 and IL-10 in venous blood. APACHE II scores were observed before treatment, 72 h and 7 d after treatment. Results: The levels of presepsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients of three poisoning groups were increased at three different time points compared with control group, while the level of IL-10 was decreased. And there were significant differences between each poisoning groups ($P<0.05$). The levels of prespsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients of death group were higher than survive group at three different time points, while the level of IL-10 was lower ($P<0.05$). The mortality rates of three poisoning groups were 28.57%, 70.27% and 92.59%, and there were significant differences between each poisoning groups ($P<0.05$). The area under curve (AUC) of presepsin level and APACHE II scores of APP patients on admission were 0.862 and 0.731, respectively. Presepsin had a better predictive ability than APACHE II score for 28-day mortality rate in APP patients ($P<0.05$). The level of presepsin was negatively correlated with survival rates ($r=0.291$, $P=0.007$). Conclusion: Monitoring the level of presepsin in serum has an important role in assessing the severity of APP patients, guiding treatment and predicting prognosis.

Keywords: Soluble CD14 subtype, presepsin, acute paraquat poisoning, APACHE II

Introduction

Paraquat (PQ) is a widely used organic heterocyclic contactive herbicide. It volatilizes quickly after spraying, which has high toxicity to humans and animals [1]. PQ can be absorbed into the body through the skin, respiratory tract and digestive tract. The absorption rate in the gastrointestinal tract is about 5 to 10% after oral administration, and the concentration reaches the peak after 1-4 h of absorption [2]. PQ can distribute to the lung, liver, kidney, thyroid, muscle through blood circulation, and cause multiple organ system dysfunction [3]. Oral lethal dose for adults is about 5-10 ml of 20% PQ solution (20-40 mg/kg).

Acute paraquat poisoning (APP) is a common type of poisoning with fast disease progression [4]. Effective antidote is lacked for PQ poisoning, and the mortality rate of oral PQ poisoning is up to more than 58% [5]. Severe APP can cause acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) [6]. Currently, there are no standardized treatments in domestic and overseas, and no sensitive biomarkers that can objectively and effectively assess the degree of disease, treatment and prognosis [7].

Soluble CD14 subtype, also known as presepsin, is a new inflammatory factor found in the body. Currently, the mortality of PQ poisoning is high without specific antidote. The poisoning mechanism of PQ is not fully understood, and it is related with inflammatory response, oxidative damage, mitochondrial damage and cell apoptosis, in which inflammatory response

Table 1. Comparison of general information between poisoning and control groups ($\bar{x}\pm s$)

Groups	Cases	Age (year)	Sex (male/female)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
Poisoning group	85	39.32±11.03	35/50	23.98±3.15	123.51±15.96	61.34±8.54
Control group	50	38.74±11.32	25/25	23.83±2.93	125.98±14.75	62.17±8.32

plays a key role in the occurrence and development of CD14. Presepsin is discovered in 2004 as a new biomarker of novel sepsis [8]. It is a glycoprotein and the main receptor that can mediates lipopolysaccharide binding protein (LBP) in neonatal sepsis. It can activate macrophages, release inflammatory factors and induce inflammatory cascade [9]. The concentration of presepsin in plasma in health people is very low. Presepsin can be induced by bacterial infection, which can activate coagulation and fibrinolysis systems, and cause septic shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome (MODS). Liu [10] found presepsin could effectively evaluate the prognosis condition of patients with severe sepsis and septic shock, which played an important role in early risk stratification of sepsis patients. Presepsin has become an effective biomarker for early diagnosis, disease classification and prognosis evaluation for emergency critically ill patients.

In this study, we analyzed the presepsin at different time points in early period to study the relationship between presepsin and the severity of the disease and prognosis of APP patients.

Material and methods

General information

From September 2013 to September 2016, we studied 85 APP patients (35 males and 50 females) who were treated in Emergency Department of Harrison International Peace Hospital Affiliated to Hebei Medical University. The age was between 17 to 49 years old with an average age of 39.32±11.03. Diagnostic criteria were referred to national occupational health standards 'Occupational acute paraquat poisoning diagnosis (GBZ246-2013)'.

Inclusion criteria: (1) Orally taking poison; (2) Having a history of taking PQ pesticides; (3) After admission, survival time >7 d; (4) Complete clinical information.

Exclusion criteria: Exclusion of patients who had severe heart and lung disease, various infectious diseases, sepsis, cerebrovascular disease, diabetes insipidus and various metabolic diseases.

All patients were initially visited in our hospital after poisoning and taken unified treatment. The specific treatments were as follows: gastric lavage, catharsis, hemoperfusion (JF-800A HP machine, Zhuhai Jianfan Biotechnology Company, China), cyclophosphamide, high-dose glucocorticoid, reduced glutathione, Vitamin E, Vitamin C, fluid infusion, rhubarb-based traditional Chinese medicine sequential treatment, and supportive treatment of organ functions.

Detection indices

Venous blood (10 ml) was collected from all APP patients before treatment, at 72 h and 7 d after treatment, and centrifuge at 3000 r/min for 10 min. Serum was collected and stored at -80°C for further use. The level of CRP was detected by Hitachi 7600 automatic biochemical analyzer. The level of TNF-α, IL-6 and IL-10 were detected by Quantikine® enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN, USA). Presepsin was detected by chemiluminescence enzyme-linked immunosorbent assay. The scores of Acute Physiology and Chronic Health Evaluation (APACHE II) and 28-day mortality rate were noted. The starting date of 28-day mortality rate was from the day of admission. The relationship between presepsin and survival rate was analyzed. APACHE II was consisted of acute physiological parameters, chronic health status, age and other components. The score ranged from 0 to 71 points. Physiological parameters are as follows: body temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, PH or HCO_3 of arterial blood, serum sodium, serum potassium, serum creatinine, leucocrit value, leukocyte count, and Glasgow coma scale. APACHE II scores were added by each item.

Table 2. Comparison of indices in control and different poisoning groups ($\bar{x}\pm s$)

Groups	Presepsin (pg/mL)			APACHE II scores			CRP (mg/L)		
	Before treatment	72 h	7 d	Before treatment	72 h	7 d	Before treatment	72 h	7 d
Control group	126.53±28.12	-	-	4.87±2.03	-	-	5.04±0.84	-	-
Light poisoning group	471.22±75.12*	322.12±66.58	263.14±47.28	8.01±3.45	6.51±3.14	5.06±1.75	25.46±6.25*	15.12±4.02	5.67±1.39
Moderate poisoning group	1030.43±330.48$^{*,\#}$	1834.87±647.64$^{\#}$	1631.52±538.07$^{\#}$	15.34±6.88$^{\#}$	21.15±9.21$^{\#}$	17.03±8.33$^{\#}$	37.18±7.54$^{*,\#}$	54.06±9.84$^{\#}$	43.21±13.28$^{\#}$
Heavy poisoning group	2875.21±1293.87$^{*,\#,\Delta}$	3247.51±1655.03$^{\#,\Delta}$	4066.71±2128.51$^{\#,\Delta}$	24.07±10.68$^{\#,\Delta}$	29.51±12.35$^{\#,\Delta}$	36.23±16.17$^{\#,\Delta}$	53.12±13.24$^{*,\#,\Delta}$	89.25±16.89$^{\#,\Delta}$	103.23±22.68$^{\#,\Delta}$

Groups	TNF-α (pg/mL)			IL-6 (pg/mL)			IL-10 (pg/mL)			Mortality rate (%)
	Before treatment	72 h	7 d	Before treatment	72 h	7 d	Before treatment	72 h	7 d	
Control group	38.12±6.78	-	-	60.01±10.95	-	-	48.06±10.25	-	-	-
Light poisoning group	67.51±10.11*	59.02±10.03	47.52±6.31	76.51±19.26*	71.55±15.28	66.34±12.19	33.54±8.98*	41.87±9.87	46.57±10.84	28.57
Moderate poisoning group	105.24±10.29$^{*,\#}$	125.85±16.34$^{\#}$	90.25±11.32$^{\#}$	97.48±25.31$^{*,\#}$	135.02±33.54$^{\#}$	143.85±33.54$^{\#}$	30.47±7.87*	25.47±6.81$^{\#}$	27.21±8.05$^{\#}$	70.27
Heavy poisoning group	215.75±48.13$^{*,\#,\Delta}$	256.64±56.97$^{\#,\Delta}$	296.87±69.75$^{\#,\Delta}$	133.95±35.97$^{*,\#,\Delta}$	190.05±37.54$^{\#,\Delta}$	215.74±43.26$^{\#,\Delta}$	27.86±8.46$^{*,\#,\Delta}$	21.81±6.76$^{\#,\Delta}$	20.84±6.12$^{\#,\Delta}$	92.59

$^{*}P<0.05$, compared with control group; $^{\#}P<0.05$, compared with light poisoning group; $^{\Delta}P<0.05$, compared with moderate poisoning group.

Table 3. Comparison of indices in survive group and death group ($\bar{x}\pm s$)

Groups	Cases	Presepsin (pg/mL)			APACHE II scores			CRP (mg/L)		
		Before treatment	72 h	7 d	Before treatment	72 h	7 d	Before treatment	72 h	7 d
Survive group	28	1318.79±608.12	1146.17±567.25	957.18±426.71	15.13±3.57	11.32±3.04	8.97±31.53	27.80±8.22	14.33±5.67	6.85±1.73
Death group	57	2395.46±948.13*	2738.12±1139.14*	3007.19±1210.98*	22.58±9.57*	27.84±12.57*	32.05±16.57*	40.21±8.56*	59.81±12.54*	88.53±12.78*

Groups	Cases	TNF-α (pg/mL)			IL-6 (pg/mL)			IL-10 (pg/mL)		
		Before treatment	72 h	7 d	Before treatment	72 h	7 d	Before treatment	72 h	7 d
Survive group	28	106.21±21.18	90.87±13.51	77.48±12.67	94.76±21.54	79.22±19.53	70.98±17.65	35.67±9.64	42.57±10.22	47.97±11.23
Death group	57	140.76±24.25*	197.35±33.71*	243.67±53.12*	123.75±33.67*	156.32±35.38*	197.38±39.45*	30.74±8.57*	27.33±8.01*	22.55±5.41*

$^{*}P<0.05$, compared with survive group.

Groups

According to PQ poisoning grading standards, patients were divided into three groups: light poisoning (21 cases, concentration of PQ <10 mg/L, in addition to gastrointestinal symptoms, also accompanied with acute moderate toxic nephropathy), moderate poisoning (37 cases, concentration of PQ 10-30 mg/L. On the basis of light poisoning, having one of the following features: 1. Acute chemical pneumonitis. 2. Acute moderate toxic nephropathy. 3. Acute moderate toxic liver disease), and heavy poisoning (27 cases, concentration of PQ >30 mg/L. On the basis of moderate poisoning, having one of the following features: 1. Acute chemical pulmonary edema. 2. ARDS. 3. Mediastinal emphysema, pneumothorax or subcutaneous emphysema. 4. Pleural effusion or diffuse pulmonary fibrosis. 5. Acute severe toxic nephropathy. 6. MODS. 7. Acute moderate or severe toxic liver disease) groups. According to the conditions of prognosis, they were divided into two groups: survive group (28 cases) and death group (57 cases), and 50 healthy subjects were as control group. The control group included 28 males and 22 females, and aged between 35 to 49 years old with an average age of 38.74±11.32.

All patients signed informed consent. The study was approved by the ethics committee of Harrison International Peace Hospital Affiliated to Hebei Medical University.

Statistical analysis

We used SPSS 17.0 for the data analysis. All independent samples showed normal distribution. All data were shown as $\bar{x}\pm s$ and analyzed by repeated measures or one-way analysis of variance. We applied t-test and χ^2 test for the comparison of intra-groups. The data of mortality rates were analyzed by the χ^2 test. Kaplan-Meier survival curve was drawn by the predictive value of APP patients analyzed by ROC curve. The differences of survive rates were analyzed by the Log Rank test. Correlation analysis were analyzed by the Pearson test, with $P<0.05$ considered statistically significant.

Results

Comparison of general information between poisoning and control groups

There were no significant differences in sex, age, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) among the poisoning groups and control group ($P>0.05$) (**Table 1**).

Comparison of indices in different poisoning groups

There were significant differences in the levels of presepsin, CRP, TNF-α, IL-6, IL-10 and scores of APACHE II in patients from different poisoning groups ($P<0.05$). There were significant differences in the levels of presepsin, CRP, TNF-α, IL-6, IL-10 and scores of APACHE II in patients before treatment, at 72 h and 7 d after treatment ($P<0.05$). The levels of presepsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients from three poisoning groups were increased at three different time points compared with control group, while the level of IL-10 was decreased. And there were significant differences between each poisoning groups ($P<0.05$). The mortality rates of three poisoning groups were 28.57%, 70.27% and 92.59%, and there were significant differences between each poisoning groups ($P<0.05$) (**Table 2**).

Comparison of indices in survive group and death group

There were significant differences in the levels of presepsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients between survive group and death group at three different time points ($P<0.05$). The levels of prespsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients of three poisoning groups were increased at three different time points compared with control group, while the level of IL-10 was decreased ($P<0.05$). The concentration of presepsin in survive group was decreased with the time, whiletheconcentrationindeathgroupwasincreased (**Table 3**).

Comparison of predictive ability for 28-day mortality rate between presepsin level and APACHE II

The AUG of presepsin was higher than APACHE II score. Presepsin had a better predictive ability than APACHE II score for 28-day mortality rate in APP patients ($P<0.05$) (**Figure 1**; **Table 4**).

Comparison of 28-day mortality rate in different poisoning groups

The 28-day survival rates in light poisoning, moderate poisoning and heavy poisoning groups were 71.43% (15/21), 29.73% (11/37),

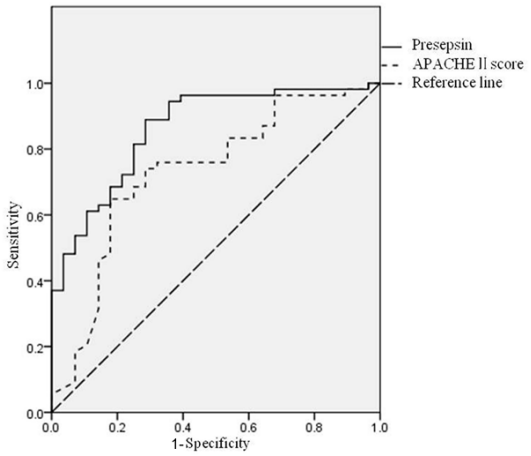

Figure 1. Receiver operating characteristic (ROC) curves of presepsin level and APACHE II score for the 28-day mortality rate in APP patients.

and 7.41% (2/27), respectively. There were significant differences in three different poisoning groups (χ^2=23.56, *P*=0.003). Kaplan-Meier survival curve showed significant differences in three different poisoning groups (Log Rank value 32.84, P=0.000) (**Figure 2**).

Correlation between presepsin level and survival rate in APP patients on admission

The lower the presepsin level in APP patients, the higher the survival rate was. The correlation analysis indicated that the level of presepsin was negatively correlated with survival rates (r=0.291, *P*=0.007) (**Figure 3**).

Discussion

The mechanism of PQ poisoning is not fully known, and the main known mechanisms includes inflammation, oxidative damage, mitochondrial damage and apoptosis [11]. Inflammation plays a vital role in the development of APP. After PQ enters our body, it can cause severe systemic inflammatory response syndrome (SIRS), induce inflammatory cytokines cascade reaction [12]. It also can activate immune cells, such as neutrophils and macrophages, so as to induce inflammatory response and pulmonary fibrosis, and secrete a large number of inflammatory mediators, such as IL-10, TNF-α, IL-6 and interleukin-8 (IL-8) [13]. APACHE II score system is one of the good indices to reflect the seriousness of critical illness in the world. It has been widely used in the evaluation and prognosis of critical illness [14]. Because the mortality rate of oral PQ poisoning is up to more than 58%, so the mortality rate is evaluated by dynamic changes of APACHE II score. In this study, the levels of presepsin, CRP, TNF-α, IL-6 and the scores of APACHE II in patients of death group were higher than survive group at three different time points, which indicated that a large number of inflammatory cells were infiltrated and cytokines were released in patients.

Currently, prognosis of APP patients is estimated by the oral dose of PQ and admission time. Patients with a large dose of PQ can show pulmonary edema and pulmonary hemorrhage within 24 h, and die in 1-3 d because of ARDS [15]. Patients not with high dose show subacute duration, and they have breath difficulties around 1 week. The symptoms reach the peak around 2-3 weeks and most patients die of respiratory failure [16]. PQ poisoning can cause acute respiratory disease, function damage of multiple organ system, which is easy to cause inflammatory response, oxidative damage, mitochondrial damage and cell apoptosis. Thus, patients with PQ poisoning are often infected with bacteria. Presepsin, as a new inflammatory factor, is related with inflammatory response, oxidative damage, mitochondrial damage and cell apoptosis. Thus, presepsin was increased by PQ poisoning. In this study, there were significant differences in 28-day mortality rate in three different poisoning groups. With the increase of the concentration of paraquat, the severity of patients gradually increased, resulting in inflammatory cascade reaction. The level of CD14 increased with a high mortality rate, which suggested that the higher level of serum presepsin on admission was, the higher mortality rate and lower survival rate were. So, APP patients should be treated as early as possible to reduce the poison concentration in blood and thus reduce the mortality rate. Hence, it is important to look for simple and effective index to evaluate the prognosis, so as to improve the survival rate.

CD14 is a high-affinity receptor of lipopolysaccharide (LPS) and lipopolysaccharide-binding protein (LBP) complex in gram-negative (G-) bacteria [9]. It has two kinds of forms: mCD14 and sCD14 [8]. sCD14 is an important pathway to mediate the response of CD14-negative cells

Table 4. The analysis of predictive ability of presepsin level and APACHE II score on 28-day mortality rate in APP patients at admission

Indices	AUG	95% CI	Critical value	Sensitivity	Specificity
Presepsin	0.859	0.783-0.951	1238.9 pg/mL	0.959	0.611
APACHE II score	0.728	0.603-0.837	15.9 scores	0.746	0.683

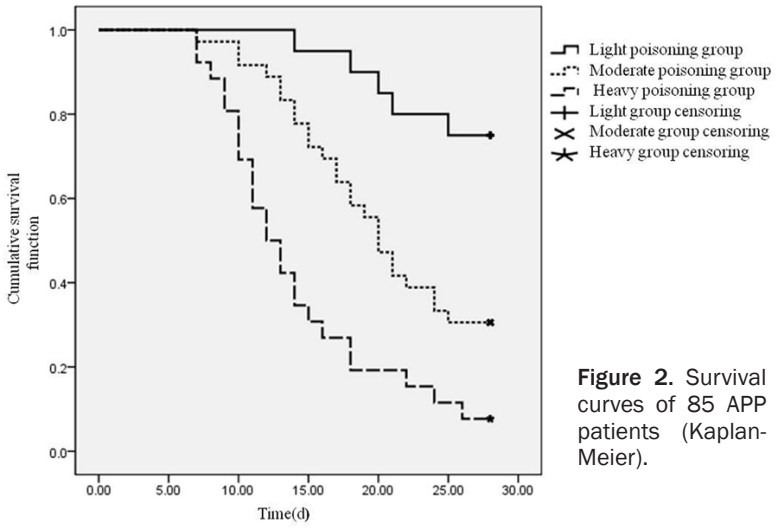

Figure 2. Survival curves of 85 APP patients (Kaplan-Meier).

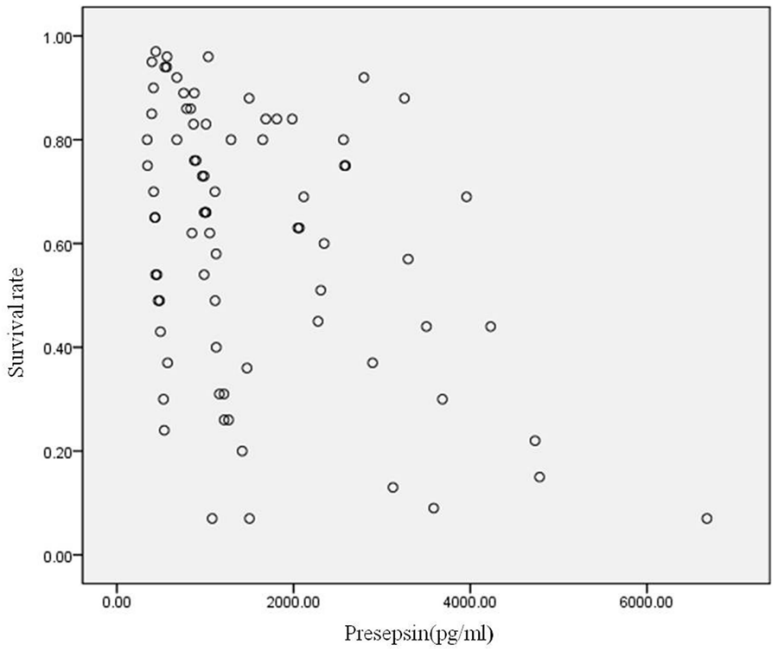

Figure 3. The correlation between presepsin level and survival rate in APP patients (n=85) on admission.

such as endothelial cells and epithelial cells. Soluble CD14 subtype is also called presepsin. It can effectively evaluate the prognosis condition of patients with severe sepsis and septic shock, which plays an important role in early risk stratification of sepsis patients. Presepsin has a high value in the early diagnosis, classification and prognosis of sepsis [17]. Emergency room physician evaluates the condition of sepsis through detecting the presepsin level, and makes early intervention to improve survival rate [18]. Although presepsin is induced by endotoxin, the concentration in pesticide poisoning patients is significantly increased according to our clinical observations. Presepsin can be detected by a kit, which is convenient, and has high sensitivity, specificity and effectiveness. Chemiluminescence enzyme immunoassays do not require pretreatment of samples, so data can be obtained in a short time [19]. The indices, such as leukocyte, bilirubin, transaminase, creatinine, and IL-18, are significantly higher 2-3 days later, and some of them are affected by a large dose of cytotoxic drugs, such as glucocorticoid and cyclophosphamide. The sensitivity of these indices is lower than presepsin [20], hence, we choose presepsin as an indicator to evaluate the condition of disease and analyze the prognosis of PQ to provide guidance for clinical treatment.

Conclusion

Presepsin can provide a reference for the early diagnosis of APP patients and monitor the dynamic changes in the treatment to adjust the treatment timely. It is important for the guidance of clinical medication. Compared to other biomarkers, there is

still no further research on presepsin. Further studies are needed to clarify the mechanism of presepsin, and to explore the preventive and protective measures to provide clinical guidance for reducing the mortality rates.

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Disclosure of conflict of interest

None.

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