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Research Paper

Identifying the Effective Factors in the Death of Patients Receiving Convalescent Plasma

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ABSTRACT

Background: Despite the fast spread of COVID-19 around the world, no definitive treatment has been found for the disease yet. Various drugs have been tried to reduce the mortality rate of the disease. In this regard, convalescent plasma therapy is a beneficial method to control the illness.

Objective: This study aims to determine the outcomes of patients receiving this therapy in Bu-Ali Hospital, Qazvin, Iran.

Methods: The present study is a case series of 60 samples. The samples were selected by purposive sampling method. The study was conducted after ethical approval and patients' consent in 2020. The inclusion criteria were having a lung scan confirming the disease by an internist or infectious disease specialist, a positive PCR test, and a history of receiving plasma during treatment.

Results: Out of 60 patients with COVID-19 who received convalescent plasma, 33 (55%) survived. The findings indicate that patients who received plasma and died were not significantly different from surviving patients regarding age, sex, underlying disease, and length of hospital stay (P>0.05). However, there was a significant difference between the deceased and surviving patients regarding plasma receiving time (P=0.005).

Conclusion: If the convalescent plasma therapy of patients starts closer to the time of admission, the effect of therapy on reducing patient mortality will be greater.

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1. Introduction

The COVID-19 disease is the largest and most severe pandemic since the 1918 flu [1], and its emergence has posed unprecedented challenges to public health [2]. Clinical manifestations in patients range from none to severe life-threatening symptoms [3]. Similar to MERS-CoV (MERS: Middle East respiratory syndrome) and SARS-CoV (SARS: severe acute respiratory syndrome), there is still no specific antiviral treatment for COVID-19 [4]. Convalescent plasma (CP) has been considered an experimental method for the treatment of patients [5]. The use of plasma was frequent before the development of vaccines [6]. The clinical benefits of this technology have been observed in previous large-scale viral epidemics such as Ebola, SARS, (MERS), the influenza pandemic, and other major infectious outbreaks [7], leading to a reduction in mortality in the patients [8]. The main reasons for favoring this treatment are our increased knowledge of infectious diseases in the early 20th century, as well as our experience with MERS, SARS, and the flu. The promising results of these studies are the basis for its use in severe cases of SARS-CoV-2 infections [9]. Data collected by Chinese scientists demonstrate the ability of CP therapy to reduce the severity and or duration of COVID-19 symptoms in humans [10]. The planned dose for CP of COVID-19 patients is from 200 mL to 1 L, but in most clinical studies, 4 mL/kg of body weight has been used [11]. In a non-randomized multicenter clinical trial in Iran, CP was administered to 115 COVID-19 patients, significantly reducing the need for intubation, length of hospital stay, and overall mortality [12]. The results of these studies allow us to answer many questions related to CP therapy [13].

In most viral diseases, the virus multiplies in the host and peaks in the first week of infection. Therefore, the initial immune response occurs 10-14 days after the time of viral infection, and if the virus continues to spread in the third week, the worsening of the clinical condition due to inflammatory attacks or hyperemia can cause serious tissue damage [14]. That is why CP should be prescribed early in the course of the disease [7].

In general, the evidence suggests that plasma from patients who have recovered from viral infections can be used as a treatment without severe side effects, and this makes CP therapy in patients with SARS-CoV worthy of research [15]. This study aimed to determine the effective factors in the death of patients receiving convalescent plasma.

2. Material and Methods

The present case series study was conducted on 60 samples. The research was done after obtaining ethical approval and patients' consent in Bu-Ali Hospital, Qazvin City, Iran, in 2020. Samples were purposefully selected from patients admitted to the intensive care unit. Also, their diseases were confirmed by internal medicine or infectious disease specialist after performing a lung scan and a positive PCR test. The inclusion criteria were aged 18 years or older, plasma intake during treatment, ICU admission, and physician confirmation of COVID-19. Patients' information was obtained by reviewing their records. The therapeutic dose for CP of COVID-19 patients was 4 mL/kg of body weight. All patients with COVID-19 received antiviral drugs and steroids simultaneously; many patients also received antibiotics and antifungals to prevent co-infections. Factors of sex, age, underlying diseases, length of hospital stay, and time of plasma injection were measured in deceased and surviving patients. The sample size was estimated using d's Cohen table to consider the correlation of the main variables of the study. Sampling was done as a census of patients receiving plasma over 6 months. Due to the low number of plasma injection cases in affected patients, 60 patients had CP therapy in this period.

After collecting data and entering them into the SPSS software, version 25, the statistical analysis of data was done using descriptive statistics (various tables and graphs) and inferential statistics (the Chi-square test, Independent samples t-test, Mann-Whitney test, and 1-way ANOVA).

Covariance analysis was used to control the effect of quantitatively confounding variables, and a randomized complete block design was used to control the effect of qualitatively confounding variables. A binary logistic regression test was also used to investigate the relationship between variables and CP therapy.

3. Results

The findings of this study showed that out of 60 patients studied, 33(55%) survived after receiving plasma and 27(45%) died. There was no significant difference between deceased and surviving patients regarding lung involvement, laboratory symptoms, or vital signs. Out of 60 patients studied, 31 were female, and 29 were male. Out of 60, 25 died (14 women and 11 men) with no significant difference in mortality between females and males (P=0.436). The mean age of patients was 55.68 years, and there was no significant relationship between mortality and the age of patients (P=0.324). The study patients

Table 1. Outcomes of COVID-19 patients receiving convalescent plasma (n=60)

Groups			Dead Patient (n=27)	Live Patient (n=33)	P
Age (y)	Mean±SD		58.08±14.67	54.27±14.86	0.324
Sex	Men		12	18	0.436
	Women		15	15	
Underlying disease	Hypertension	Yes	12	8	0.099
		No	15	25	
	Pulmonary disease	Yes	5	1	0.047
		No	22	32	
	Heart disease	Yes	5	3	0.285
		No	22	30	
	Diabetes mellitus	Yes	6	8	0.854
		No	21	25	
Duration of hospitalization (d)	Mean±SD		13.81±12.78	13.36±10.27	0.888
Plasma injection time (d)	Mean±SD		6.76±7.28	3.63±3.45	0.005

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had 14 patients with diabetes and 46 patients without diabetes, which were not significantly different in terms of mortality (P=0.854). In terms of blood pressure, 40 people did not have the disease, and 20 people had high blood pressure, but there was no significant difference in mortality (P=0.099). Out of 60 patients, 6 patients had underlying respiratory diseases, and 54 patients had no underlying respiratory diseases. These two groups did not differ significantly in the incidence of death (P=0.047). The mean length of hospital stay in surviving patients was 13.36 days. The mean length of hospital stay was 13.81 days in deceased patients. There was no significant difference (P=0.88) between the two groups in this group. The results showed that the closer the time of CP therapy to the time of hospitalization, the lower would be the mortality rate (P=0.005). The statistical result of the binary logistic regression also confirms the relationship between CP therapy and mortality rate, and the closer the CP therapy time to the hospitalization time, the lower the mortality rate (P=0.0009) (Table 1 and 2).

4. Discussion

The study results showed that the closer the time of CP therapy to the time of hospitalization of patients, the results will be better. Some studies show that CP containing large amounts of neutralizing antibodies can remove the pathogen from the patient's circulation [16]. A reduction in mortality following CP therapy in patients with COVID-19 has been reported in many studies, including those done by Janiaud et al. [17]. In the present study, 45% of plasma recipients died, so the factors affecting the increase in mortality of patients receiving plasma were investigated.

Table 2. Regression logistic hospitalization interval until plasma injection

Variables	B	SE	Wald	df	P	OR	95% CI for Exp(B)	
							Lower	Upper
Plasma injection time	-0.258	0.099	6.739	1	0.009	0.773	0.636	0.939
Constant	0.676	0.489	1.907	1	0.167	1.966		

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The effect of plasma alone cannot be determined because patients have received several other drugs (including antiviral drugs) [18].

Of 60 patients, 27 died, of which 14 were women and 11 were men. There was no significant difference in mortality rates between men and women. In the study of Sepandi et al., the mortality rate was higher in the studied men, probably due to the presence of the X chromosome and male hormones [19]. The difference in mortality rates between the sexes is also influenced by factors such as the appropriate immune response and underlying diseases [20]. In this study, the numbers of men and women who died were almost equal, and according to statistical findings, the prevalence of the underlying disease among men and women did not significantly differ.

In many studies, the relationship between mortality and age has been investigated. In this study, no significant relationship was found between death and the age of patients. In the study of Joyner et al., one of the important factors influencing the death of patients receiving plasma was the age of patients [21]. Various factors affect the mortality rate at different ages in different communities, including the quality of health care systems, but in many countries, the highest mortality rate from COVID-19 has been in those aged 60-69 [22]. In our study, the average age of patients was about 60, so compared to some studies, the average age of the deceased is high.

This study showed no significant relationship between underlying diseases, including diabetes, hypertension, chronic respiratory diseases, and heart disease, and the incidence of death in patients receiving plasma. In their study, Ibrahim et al. found that CP therapy increased survival in diabetic patients and patients with chronic liver problems [23]. In many studies, an underlying disease has been mentioned as a factor for increased mortality and hospitalization in the intensive care unit [24], among which diabetes, hypertension, renal, and cardiovascular diseases have a higher share [19]. In several studies, in addition to diabetes and kidney disease, cerebrovascular disease, obesity, and immunosuppressive diseases have also been mentioned as effective factors in increasing hospitalization and mortality [24]

Ibrahim et al. concluded that plasma reduced the length of hospital stay in patients receiving plasma [25]. In this study, there was no significant relationship between plasma intake and the length of hospital stay. Janiad et al. found the same result as our study [18].

Studies on the effectiveness of convalescent plasma put much emphasis on the time of CP therapy. It is well-documented that the faster the plasma injection occurs, the better the effect on patient outcomes [13]. The study by Key down et al. mentioned 3 days after admission as the best time for CP therapy [16]. In this study, the mean CP therapy time was 5 days after hospitalization. The relationship between CP therapy time and the patient mortality rate was significant. However, there was no significant relationship between the time of death and CP therapy in patients. In addition to the effect of CP therapy time on the treatment of COVID-19 patients, factors such as plasma collection time and antibody titer in plasma are also very important.

Our study has several limitations. Several patients received combination therapies that may be involved in clearing the virus. It is suggested that a two-group study be compared with the two treatments.

5. Conclusion

About 55% of the patients survived after plasma injection. Also, patients who received plasma shortly after admission into the hospital were more likely to survive. The sooner plasma is injected, that is, during the early days of hospitalization, the better would be the clinical outcome in patients with COVID-19.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Ethics Committee of Qazvin University of Medical Sciences (Code: IR.QUMS.REC.1399.125). In this article, the names of patients were kept anonymous. The patients and their families were given sufficient information about the study, and the confidentiality of personal information was assured.

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Authors' contributions

Investigation: Leili Yekeh Fallah and Sareh Mohammadi; Data collection: Peyman Namdar, Leili Yekeh Fallah, and Sareh Mohammadi; Writing – review & editing: Saeedeh Mouri; Conceptualization and Supervision: Sareh Mohammadi.

Conflict of interest

The authors declared no conflict of interest.

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