

Therapeutic Plasma Exchange Application in the Treatment of Sepsis in A Pediatric Burn Center

Çocuk Yanık Merkezinde Sepsis Tedavisinde Terapötik Plazma Değişimi Uygulaması

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ABSTRACT

Objective: In our study, we aimed to analyze the use of Therapeutic plasma exchange (TPE) in the management of septic and Thrombocytopenia-associated multiple-organ failure (TAMOF) in the burn intensive care unit of a children's hospital retrospectively.

Material and Methods: Demographic, clinical, and laboratory data of the pediatric burn patients who were applied TPE between 1 January 2016 and 1 January 2021 were obtained from the hospital information system and medical records and analyzed. The patients were divided into two groups those who died during follow-up and those who recovered.

Results: TPE was performed on 14 burned children (Boy: Girl 5:9). The median age of the patients was 6,6 years (range 1-18 years). The mean TBSA of the patients was 47.76% (20-75). The most common cause of burns was flame burn. The mean hospital stay of the patients was 18.4±12.6 (7-94) days.

4 patients in group 1 recovered and 10 patients in group 2 died during follow-up. There was no statistical difference between the groups in terms of age, gender, and TBSA ($p=0.590$, 0.890 , 0.990). We determined that patients in group 2 were statistically higher in terms of MODS ($p=0.030$), Pelod score ($p=0.001$), and expected death rate according to Pelod score ($p=0.003$). It was observed that the application of TPE in the first 24 hours after the occurrence of TAMOF significantly reduced mortality ($p=0.010$).

Conclusion: TPE should be used as an additional treatment method to conventional therapy in critically ill patients in pediatric burn intensive care units. TPE application in the first 24 hours after the occurrence of TAMOF reduces mortality.

Key Words: Child, Intensive care, TAMOF, Plasma exchange

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Öz

Amaç: Çalışmamızda, bir çocuk hastanesinde yanık yoğun bakım ünitesinde septik ve Trombositopeni ile ilişkili çoklu organ yetmezliği (TAMOF) tedavisinde Terapötik plazma değişimi (TPE) kullanımını geriye dönük olarak incelemeyi amaçladık.

Gereç ve Yöntemler: 1 Ocak 2016-1 Ocak 2021 tarihleri arasında TPE uygulanan yanık çocuk hastalarının demografik, klinik ve laboratuvar verileri hastane bilgi sistemi ve tıbbi kayıtlarından elde edilerek incelendi. Hastalar takipte ölenler ve iyileşenler olarak iki gruba ayrıldı.

Bulgular: 14 yanık çocuk hastaya (Erkek:Kadın5:9) TPE yapıldı. Hastaların ortalama yaşı 6.6 yıl (1-18 yıl)'di. Hastaların ortalama TBSA'sı %47.76 (20-75)'di. En sık yanık nedeni alev yanığıydı. Hasta-ların ortalama hastanede kalış süreleri 18.4±12.6 (7-94) gündü.

Grup 1'de iyileşen 4 hasta ve grup 2'de takip sırasında ölen 10 hasta vardı. Gruplar arasında yaş, cinsiyet ve TBSA açısından istatistiksel fark yoktu ($p=0.590$, 0.890 , 0.990). Grup 2'deki hastaların MODS ($p=0.030$), Pelod skoru ($p=0.001$) ve Pelod skoruna göre beklenen ölüm oranı ($p=0.003$) açısından istatistiksel olarak daha yüksek olduğunu belirledik. TAMOF oluştuktan sonraki ilk 24 saat içinde TPE uygulamasının mortaliteyi anlamlı derecede azalttığı gözlemlendi ($p=0.010$).

Sonuç: Çocuk yanık yoğun bakım ünitelerindeki kritik hastalarda TPE konvansiyonel tedaviye ek bir teda-vi yöntemi olarak kullanılabilir. TAMOF oluştuktan sonraki ilk 24 saat içinde TPE uygulaması mortaliteyi azaltmaktadır.

Anahtar Sözcükler: Çocuk, Yoğun bakım, TAMOF, Plazma değişimi

INTRODUCTION

Burn is a serious trauma with high morbidity and mortality. Deterioration of skin integrity as a result of burns may lead to the entry of microorganisms into the body and thus the development of invasive infections (1). In addition, necrotic tissues formed after burns form a suitable medium for the growth of microorganisms. The risk of infection is increased in burn patients due to many factors such as heat damage, applied invasive procedures, presence of a catheter, colonization of the burn wound, translocation of the gastrointestinal microbiota, and long hospital stay (2,3).

Infections in burn patients can lead to sepsis and multiorgan failure. The traditional treatment of sepsis consists of supportive treatments such as control of the source of infection, intravenous antibiotic therapy, fluid replacement, use of inotropic drugs, and mechanical ventilation (4). Despite improvements in the follow-up and treatment of patients with sepsis and multi-organ failure, mortality and morbidity rates are still high (5,6). The benefit of therapeutic plasma exchange (TPE), especially in cases of thrombocytopenia-related organ failure (TAMOF), has been demonstrated by increasing evidence in recent years (5,6).

TPE is the process of separating the patient's plasma from whole blood with the help of a medical device and replacing it with albumin and/or fresh frozen plasma from healthy donors (7, 8). TPE removes thrombogenic and antifibrinolytic molecules and replaces missing anticoagulants and profibrinolytic molecules, providing normal hemostasis, and removing cytokines and mediators that may cause organ failure (9).

Studies show that TPE treatment in patients with sepsis and TAMOF causes a decrease in mortality rates compared to those who do not (10,11). In the literature, studies on the application of TPE in pediatric burns are limited. In our study, we aimed to share the results of TPE applied to pediatric burn patients with sepsis and TAMOF in our pediatric burn center and our experience.

MATERIAL and METHODS

Between January 2016 and January 2021, pediatric patients who underwent TPE due to burn-related sepsis and TAMOF in our pediatric burn center were included in the study. The patients were divided into two groups those who died during follow-up and those who recovered. who recovered. Groups were analyzed and compared retrospectively in terms of demographic data, total burn surface area(TBSA), burn factor, length of hospital stay, Multiple organ dysfunction score (MODS), Pediatric Logistic Organ Dysfunction (PELOD) score, expected mortality rates according to PELOD score, starting day of TPE application after TAMOF, number of TPE session, complications and mortality. Both electronic and physical files of the patients were scanned retrospectively. Approval was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (No: E2-21-437, Date: 13/10/2021).

TPE was performed with the Fresenius Cup COM.TEC® device. The volume of plasma to be used; was calculated with the blood volume (patient weight x70) x (1-hematocrit) formula. 1-1.5 times the calculated plasma volume was used as replacement fluid. Transactions; It was done with fresh frozen plasma and/or albumin. Acid citrate dextrose (1:10-1:20 dilution) was used for the anticoagulation of the system. Prophylactic calcium gluconate infusion (1 mg/kg) was administered through a separate intravenous line during the procedure. All processes were performed using the cell separator centrifugation method. TPE session for each patient was determined by observing the course of the disease and clinical improvement. The patients were followed up by monitoring their vital signs throughout the TPE procedure. Consent was obtained from the parents of the patients included in the study.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 21 (SPSS Inc. Chicago, IL, USA). For the patients with numerical variables, age, length of stay, and localization, whether they were normally distributed or not was investigated with normality tests. The

differences between the groups were investigated using the Student-T test for normally distributed numerical variables and the Mann-Whitney U test for those not normally distributed. $p < 0.05$ was considered significant for all variables.

RESULTS

14 pediatric burn patients followed in the pediatric burn intensive care unit due to sepsis and TAMOF were included in the study. The mean age of the patients was 6.6 (1-18) years, five of them were (35.7%) girls and nine were (64.3%) boys. The mean TBSA of the patients was 47.76% (20-75). The most common cause of burns was flame burn ($n=8$), and the other factors were hot milk, scalding, and electrical burns, respectively. *Pseudomonas aeruginosa* ($n=9$, 64.28%) was the most common cause of sepsis in blood and wound cultures. Other microorganisms were *Acinetobacter baumannii* ($n=4$) and *klebsiella pneumonia* ($n=2$). Five (35.7%) patients were referred to our center due to burn-related sepsis from the other centers. The mean length of hospital stay of the patients was 18.4 ± 12.6 (7-94) days. The mean expected mortality rate according to the PELOD score of the patients was 90.64 ± 5.6 . Four patients who underwent TPE recovered (28.5%). The mean expected mortality rate of these four patients according to the PELOD score was $83.30 (\pm 8.04)$.

The patients were divided into two groups group 1 who recovered ($n=4$) and group 2 who died during the follow-up ($n=10$). The data of the patients, Multiple organ dysfunction score (MODS), PELOD (pediatric logistic organ dysfunction) score, expected mortality rates according to the PELOD score, the start day of TPE application after TAMOF occurs, and the number of TPE sessions according to the groups are shown in Table I. No complication was observed during TPE application in both groups.

When the patients were examined in terms of TPE application time, we observed that one of the three patients who underwent TPE with conventional treatments in the first 24 hours after the

TAMOF occurrence, died (33.3%). After 24 hours, nine of 11 patients who underwent TPE died (81.8%). It was observed that the application of TPE in the first 24 hours after the TAMOF occurrence significantly reduced mortality ($p=0.010$). All ex-patients were referred to our center due to sepsis on the multiple days of hospitalization from another center.

DISCUSSION

In sepsis, exogenous microbial agents cause the release of cytokines, chemokines, and other pro-inflammatory mediators from polymorphonuclear leukocytes and macrophages. In this process, depending on the released cytokines and mediators, an inflammatory response occurs that damages the host itself, and despite appropriate antimicrobial therapy and hemodynamic support, multiple organ failure and death may occur (12). Many studies demonstrate that TPE serves a beneficial role in the challenging burn resuscitation so TPE should be used as a useful tool in the management of severe burn septic shock (13-15).

TPE is an uncommonly used modality that has been used for rescue therapy. It is a form of extracorporeal blood purification, or component separation (apheresis), designed to remove large-molecular-weight solutes such as inflammatory mediators from the circulating blood volume (16). TPE has been used successfully to treat a wide variety of disease processes over the past 40 years, including many autoimmune disorders and inflammatory-mediated conditions (17-20). This success in treating autoimmune has led to the investigation of potential benefits of the use of TPE in many conditions commonly encountered in burn centers. The most recent American Society of Apheresis guidelines gives a level C evidence recommendation for use of TPE in sepsis-induced multiple organ failure, indicating that TPE may be used on an individual basis and acknowledging the need for the generation of more evidence (9).

Table I: The data according to the groups.

	Grup 1 (Full recovery cases)	Grup 2 (Ex cases)	p
n	4	10	
Sex (f:m)	01:03	04:06	0.590
Mean of the age	6.00 (± 5.59)	6.45 (± 5.37)	0.890
Mean of TBSA	47.75 (± 11.44)	47.80 (± 20.48)	0.990
Mean of the MODS (Multiple Organ Dysfunction Score)	9.75 (± 1.70)	13.40 (± 2.71)	0.030
Mean of the PELOD score	31.75 (± 2.87)	44.70 (± 4.16)	0.001
Mean of the expected mortality rate due to PELOD score	83.30 (± 8.04)	93.58 (± 2.90)	0.003
Mean of TPE session per case	3.5 (± 1.73)	2.14 (± 0.87)	0.060
Mean TPE starting day after onset of sepsis	5.25 (± 8.34)	8.45 (± 7.74)	0.240
Mean of the length of hospital stay	27.45 (± 8.34)	15.45 (± 8.34)	0.040

In the literature, there are few studies on the efficacy of TPE in sepsis in children (21). It has been reported that the levels of dead leukocytes in the blood taken from patients with sepsis are significantly higher and that high levels of dead leukocytes in the blood are positively correlated with the severity of organ dysfunction (22). It has been reported that TPE provides a significant decrease in the concentration of dead leukocytes in the blood and that organ failure can be protected by this mechanism (22). In a study, it was shown that TPE performed in pediatric patients with culture-positive sepsis and thrombocytopenia-related multi-organ failure reduced the organ damage score and improved 28-day survival rates (23). In another study, it was shown that TPE significantly reduced the mortality rate in pediatric patients with sepsis with multi-organ failure and thrombocytopenia compared to those who did not (24). The risk of sepsis and TAMOF and mortality increase in burn patients with a larger TBSA area (25,26). In a review of the literature, the mean TBSA of patients who developed sepsis due to burns and who was applied TPE in the treatment was 46.33 (37-52.2) (16). In our study, the mean TBSA of patients who was applied TPE was 47.76% (20-75). There was no significant difference between the groups in terms of mortality and the TBSA relationship ($p=0.99$).

In the literature, infections and related complications have been reported as the most common cause of mortality in pediatric burns (27,28). *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus* species, and *Candida* species are prominent as microorganisms causing mortality (28). In our study, the microorganisms in blood and wound cultures were *pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, consistent with the literature.

MODS and PELOD score are calculated with the clinical and laboratory parameters of patients with sepsis and TAMOF, and the expected mortality rate for the patient is calculated (29). In our study, it was found that the mean MODS, PELOD score and the expected mortality rate according to the PELOD score were statistically higher in group 2.

There is still no consensus on the timing of TPE and studies are limited. Kawai et al. (30) also showed that in children with TAMOF, those who underwent TPE in the early period had a greater improvement in organ dysfunction and the need for inotropic agents decreased earlier than in those who underwent late TPE. In a study about the experience of TPE application in children with neutropenic sepsis, it was reported that the clinical course of patients with bacterial sepsis progressed faster and was mortal than in other patients, and TPE application was recommended in children with bacterial sepsis in the earlier period (31). In our study, we determined that the application of TPE in the first 24 hours after the TAMOF occurrence significantly reduced mortality ($p=0.010$).

Complications such as urticarial reactions, citrate-related hypocalcemia, catheter-related thrombosis, bleeding, infection,

and transfusion-related lung injury may occur (32). Any complication was observed during TPE application in both groups.

CONCLUSION

In conclusion; TPE, which is an adjunct to the conventional treatment of pediatric burn patients who develop sepsis and TAMOF and do not respond to conventional treatment, is an important supportive treatment. Considering the hemodynamics and laboratory parameters of pediatric patients, it can be safely applied in intensive-care conditions. TPE applied in the first 24 hours after the TAMOF occurrence reduces mortality. Therefore, we think that TPE should be applied earlier. Prospective, randomized-controlled large series studies should be done.

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