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Plasma Exchange in Critically Ill Children: A Single-center Experience

Kritik Hastalığı Olan Çocuklarda Plazma Değişimi: Tek Merkez Deneyimi

Halil Keskin[1], Muhammet Şükrü Paksu[2], Nazik Yener[2], Özlem Temel Köksoy[2], İbrahim Kartal[3], Canan Albayrak[3], Davut Albayrak[3]

[1]Atatürk University Faculty of Medicine, Division of Pediatric Intensive Care Unit, Erzurum, Turkey
[2]Ondokuz Mayıs University Faculty of Medicine, Division of Pediatric Intensive Care, Samsun, Turkey
[3]Ondokuz Mayıs University Faculty of Medicine, Division of Pediatric Hematology, Samsun, Turkey

Abstract

Introduction: The aim of this study was to identify demographic and clinical characteristics of patients who were subjected to plasma exchange (PE) at our unit, and to investigate the effect of these factors on treatment outcome and patient prognosis.
Methods: Demographic, clinical and laboratory data of patients who were subjected to PE between January 2012 and August 2015 were obtained from the hospital information system, medical records and the records of apheresis unit.
Results: Plasma exchange was performed in 40 patients for 168 times throughout the study. The median age of the patients was 9.4 (range: 1.5-17.3) years, with a male/female ratio of 1.35. Of the patients, 47.5% had an underlying disease. The most common comorbidity was malignancy. The most common indication for PE was sepsis-related multiple organ failure (n=19, 47.5%). The mortality rate was higher in patients with an underlying chronic disease, compared to those without (25% and 7.5%, respectively). No life-threatening complication associated with the apheresis procedure was observed.
Conclusion: Our results suggest that PE can be safely performed in children. It seems that indication for PE and the presence of underlying diseases are affecting the mortality rate.
Keywords: Plasma exchange, critical patient, child

Öz

Giriş: Bu çalışmanın amacı ünitemizde plazma değişimi (PD) uygulanan hastaların demografik ve klinik özelliklerinin belirlenmesi, tedavi sonuçları ve hasta prognozları ile bunlara etki eden faktörlerin araştırılmasıdır.
Yöntemler: Ocak 2012 - Ağustos 2015 tarihleri arasında PD uygulanan hastalara ait demografik, klinik ve laboratuvar veriler hastane otomasyon sistemi, hasta dosyaları ve aferez ünitesi kayıtlarından elde edildi.
Bulgular: Çalışma süresinde 40 hastaya toplam 168 defa PD uygulanmıştı. Hastaların ortanca yaşı 9,4 (1,5-17,3) yıl, erkek/kız oranı 1,35 idi. Olguların %47,5'i altta yatan bir hastalığa sahipti. En sık komorbid hastalık malignite idi. En sık PD endikasyonu sepsis ilişkili çoklu organ yetmezliği (19 hasta, %47,5) olarak bulundu. Altta yatan kronik bir hastalığı olanlarda ölüm oranı olmayanlara göre daha yüksekti (sırası ile %25 ve %7,5). Hiçbir hastada aferez işlemi ile ilişkili yaşamı tehdit edici bir komplikasyon gelişmemişti.
Sonuç: Sonuçlarımız PD'nin çocuk hastalarda güvenle yapılabileceğini göstermektedir. Mortaliteyi etkileyen iki temel faktör PD endikasyonu ve altta yatan hastalık varlığı olarak bulunmuştur.
Anahtar Kelimeler: Plazma değişimi, kritik hasta, çocuk

Introduction

Plasma exchange (PE) is the process in which plasma is exchanged with externally administered plasma or albumin for treatment purposes.[1] It is one of the most common methods of therapeutic apheresis, and it can be life-saving in appropriate indications. In 2013, the American Society for Apheresis (ASFA) updated indications for therapeutic apheresis and classified them into four categories.[1] In addition to the ASFA guidelines, the majority of the existing data on PE have been obtained from adult studies. Although studies are limited,[2] experiences obtained from children indicate that PE is reliable in case of appropriate indications.[3] Implementation of PE in pediatric intensive care units (PICUs) has increased lately. Furthermore, many diseases and conditions have been reported which are not included in the ASFA categories, but the efficacy of therapeutic apheresis has been presented as case reports or series.[4-7] The aim of this study was to identify demographic and clinical characteristics of patients who were

Address for Correspondence/Yazışma Adresi: Halil Keskin MD, Atatürk University Faculty of Medicine, Division of Pediatric Intensive Care, Erzurum, Turkey
Phone: +90 533 434 67 34 **E-mail:** keskinpediatrize@gmail.com **ORCID ID:** orcid.org/0000-0003-4491-1327
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subjected to PE in the PICU at a tertiary university hospital and to evaluate treatment indications, the efficacy and outcome of treatment, and patient prognosis.

Materials and Methods

The study was performed in the 200-bed children hospital of our university. A retrospective analysis was performed in patients who were subjected to PE between 01.01.2012 and 15.08.2015 in the PICU. Patient data were obtained from medical record of the patients, the hospital information system, and from the apheresis unit files. Approval for the study was obtained from the local ethics committee (2015/363). The study was conducted in accordance with the principles of the Declaration of Helsinki.

In all patients, indications for PE were determined by a committee including the staff of PICU, apheresis unit and departments related to the primary disease if present. The procedure was carried out using the Spectra Optia apheresis device. Acid-citrate-dextrose (ACD) solution was used in all procedures as an anticoagulant. Replacement with fresh frozen plasma (FFP) was performed for indications such as sepsis and hemophagocytic lymphohistiocytosis (HLH), or in the presence of bleeding-causing comorbid diseases such as malignancies or aplastic anemia. Either FFP or albumin was chosen in the remaining patients. Dialysis catheter, placed in a central vein according to age and weight of patients, was used for the procedures.

The age, sex, PICU diagnosis, underlying disease if present, PE indication, number of procedures, complications associated with the procedure, and prognosis of the patients were recorded. Mean ± SD was given for numerical data and number and percent were given for nominal data. Deaths occurred within seven days after the procedure were recorded as PE-associated mortality.

Results

Plasma exchange was performed in 40 patients for 168 times throughout the study. Clinical and demographic characteristics of the patients are demonstrated in Table 1.

The most common indications for PE were sepsis-related multiple organ failure (MOF) and HLH. Most of the patients had indications from ASFA III category (n=22) (Table 2).

Complications developed during a total of 18 sessions. The procedure was terminated in three of these. The most common complications were allergic reactions against blood products and catheter occlusion. Two of the complications which led to termination of the procedure were catheter occlusion, while the other one involved allergic reaction which occurred as shivering and respiratory distress. No life-threatening complication associated with the apheresis procedure was reported to develop in any of the patients (Table 3).

The mortality rate on the 28th day of our study was 37.5%. Procedure-related mortality rate was 32.5% (n=13), and 10 of these 13 patients had an underlying chronic disease.

Three patients had no comorbid disease, and only one session of PE was carried out in two of them. The mortality rate was found to be higher in patients with comorbidity, compared to

Table 1. Clinical and demographic characteristics of the patients

Age (year) [median (minimum-maximum)]	9.4 (1.5-17.3)
Male [number (%)]	23 (57.5%)
Comorbid disease [number (%)]	19 (47.5%)
Malignancy (ALL, AML, Wilms tm)	14 (74.0%)
CHARGE syndrome	1 (5.2%)
Chronic renal failure	1 (5.2%)
Chronic granulomatous disease	1 (5.2%)
Sarcoidosis	1 (5.2%)
Thalassemia major	1 (5.2%)
Diagnosis on PICU admission [number (%)]	
Sepsis related multipple organ failure	19 (47.5%)
Hemophagocytic lymphohystiocytosis	9 (22.5%)
Encephalopathy	4 (10%)
Guillain-Barre syndrome	2 (5.0%)
Myasthenic crisis	2 (5.0%)
Thrombotic microangiopathy, HSCT associated	2 (5.0%)
Aplastic crisis	1 (2.5%)
Atypical hemolytic uremic syndrome	1 (2.5%)

ALL: Acute lymphoblastic leukemia, AML: Acute miyeloid leukemia, HSCT: Hematopoetic stem cell transplantation, PICU: Pediatric intensive care units

Table 2. Indications for PE and ASFA categories

Cases	Case number (n,%)	Sessions (n,%)	ASFA
Sepsis related MOF	19 (47.5%)	66 (39.3%)	III
Hemophagocytic lymphohystiocytosis	9 (22.5%)	44 (26.1%)	*
Guillain-Barre syndrome	2 (5%)	11 (6.5%)	I
Myasthenic crisis	2 (5%)	13 (7.7%)	I
Toxic-methabolic encephalopathy	2 (5%)	7 (4.2%)	*
Refractory status epilepticus	1 (2.5%)	2 (1.2%)	*
Autoimmune encephalitis	1 (2.5%)	5 (3.1%)	*
HSCT associated thrombotic microangiopathy	2 (5%)	16 (9.5%)	III
Atypical hemolytic uremic syndrome	1 (2.5%)	1 (0.6%)	II
Aplastic anemia	1 (2.5%)	3 (1.8%)	III

*Not included in ASFA 2013 categories, MOF: Multiple organ failure, HSCT: Hematopoetic stem cell transplantation, ASFA: American Society for Apheresis

those without (25% and 7.5%, respectively). The mortality rate in sepsis-related MOF, that was the most common indication for PE, was distinctly higher in the presence of comorbidity, compared to absence of any underlying disease (20% and 2%, respectively). The survival rates in all patients and patients who underwent PE due to sepsis-related MOF, according to the presence of an underlying disease are shown in Table 4.

The demographic and clinical characteristics, PE indication, number of procedures and the ASFA categories in deceased patients are shown in Table 5.

Plasma exchange was performed in 13 patients who did not meet the ASFA category criteria; HLH (n=9), toxic-metabolic encephalopathy (n=2), refractory status epilepticus (n=1), and autoimmune encephalitis (n=1). None of these patients died.

Table 3. Complications which developed during apheresis

	Complication		Incomplete procedure
	Number (n)	Ratio (%)	Number (n)
Allergic reaction	9	5.4	1
Catheter occlusion	6	3.6	2
Hypocalcemia	2	1.2	0
Hypotension	1	0.6	0
Total	18	10.8	3

Table 4. Survival rates in patients with Sepsis related multiple organ failure and others according to the presence of underlying disease

	With underlying disease		Without underlying disease	
	Sepsis related MOF	All cases	Sepsis related MOF	All cases
Survived	4 (10%)	9 (22.5%)	5 (12.5%)	18 (45%)
Deceased	8 (20%)	10 (25%)	2 (5%)	3 (7.5%)
Total	12 (30%)	19 (47.5%)	7 (17.5%)	21 (52.5%)

MOF: Multiple organ failure

Discussion

Although PE and plasmapheresis are often used interchangeably to refer the same condition, the two entities differ from each other. In plasmapheresis, blood is separated into two portions as cells and plasma. Then, some selected components in plasma are filtered and the remaining plasma is returned to the patient. On the other hand, PE entails the separation of blood into cells and plasma, after which patient plasma is exchanged with donor plasma or albumin while returning cells are returned into the patient.[1] In all patients in our study, PE was performed by using donor plasma or albumin.

Although, implementation of PE is increasing in Turkey and the rest of the world, experiences in children are limited. The majority of information about this subject has been obtained from adult PE cases.[8] Most cases of pediatric PE are performed in the PICU due to the need for a central vascular route, need for continuous monitoring, and due to some other factors such as underlying severe diseases.

In 2013, the ASFA updated indications for PE and grouped them into four categories. Accordingly, the ASFA-I category of diseases includes disorders where PE is accepted as primary therapy or as supplementary to the primary therapy; the ASFA-II category of diseases includes disorders where apheresis is used alone or in conjunction with other treatment as second-line therapy; the ASFA-III category of diseases includes disorders where the ideal role of therapeutic apheresis has not been established and

Table 5. Demographic and clinical characteristics and the American Society for Apheresis categories of deceased patients

Patient no	Age (year)	Underlying disease	Indication for PE	Seance number	ASFA
1	15.9	ALL	Sepsis related MOF	5	III
2	17.3	ALL	Sepsis related MOF	4	III
3	3.4	ALL	Sepsis related MOF	2	III
4	16.2	ALL	Sepsis related MOF	6	III
5	15	AML	Sepsis related MOF	3	III
6	8.3	Wilms tumor	Sepsis related MOF	1	III
7	12.3	CRF	Sepsis related MOF	3	III
8	3.6	CHARGE syndrom	Sepsis related MOF	5	III
9	14.6	-	Sepsis related MOF	1	III
10	16.3	-	Sepsis related MOF	5	III
11	8.5	ALL	Aplastic anemia	3	III
12	1.9	AML	HSCT associated thrombotic microangiopathy	6	III
13	1.6	-	Atypical HUS	1	II

ALL: Acute lymphoblastic leukemia, AML: Acute miyeloid leukemia, CRF: Chronic renal failure, MOF: Multiple organ failure, HSCT: Hematopoetic stem cell transplantation, HUS: Hemolytic uremic syndrom, ASFA: American Society for Apheresis

where the procedure is case-specific; on the other hand, the ASFA-IV category of diseases includes suggested or known disorders where therapeutic apheresis has been shown to be ineffective or harmful. Therapeutic apheresis in this category is performed only under approved study protocols.[1]

Apart from the well-defined suggestions outlined in the ASFA 2013 guidelines,[1] in many other life-threatening conditions which have been non-responsive to standard treatment, such as HLH, refractory status epilepticus, and toxic-metabolic encephalopathy, it has been reported that PE might be beneficial.[4,6,9]

As a matter of fact, during data collection for the present study, HLH was not included in the ASFA guideline,[1] but recommended for the ASFA III category in the ASFA guidelines published in 2016.[10] On the other hand, atypical hemolytic uremic syndrome (HUS) which was previously in the ASFA II category of the former guidelines has been removed from the ASFA category.[10] In our study, PE was also performed in one patient due to atypical HUS. Only one session could be carried out in this patient before death.

In our study, PE was performed in 13 patients with four indications which were not included in the 2013 ASFA category. None of these 13 patients, of whom nine had HLH which is currently included in the ASFA III category, died. The results of our study may serve as prior information for prospective studies conducted on children and concerning other indications not currently included in the ASFA classification.

Many complications associated with the PE procedure have been described.[11] In our study, the incidence of complications which necessitated discontinuation of the procedure was found to be very low. In none of the patients, a procedure-related life-threatening complication such as sepsis, thrombosis, pneumothorax, hematoma, air embolism, arterial injury, hemolysis, coagulopathy, transfusion-related acute lung injury and anaphylactoid reaction developed.

There was an underlying disease in 10 of 13 patients who died, and in 12 of them the category of PE indication was in ASFA III. In two of three patients without any underlying disease who died, indication for PE was sepsis-related MOF. These were the most remarkable findings in our study.

The mortality rate was found to be high in patients who were subjected to PE due to sepsis-related MOF. The reason for this may be the fact that we performed PE as a salvage therapy in patients who were non-responsive to all previous treatments. Moreover, the mortality rate in patients with an underlying disease was found to be higher than in patients without, as it was noted in previous studies.[12,13]

Study Limitations

Relatively small sample size and its retrospective design are the limitations of our study.

Conclusion

In conclusion, our study results show that PE is a safe treatment method for critically ill children with the appropriate indication, and that the treatment is more effective in patients without comorbidity in addition to PE indication. In addition, we suggest that there are also other diseases which may be recommended in the further ASFA guidelines. However, further large-scale, prospective studies are required to shed light on this subject.

Ethics

Ethics Committee Approval: Ondokuz Mayıs University Clinical Research Ethics Committee (2015/363).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ş.P., N.Y., Ö.T.K., İ.K., C.A., D.A., Concept: M.Ş.P., N.Y., Ö.T.K., İ.K., C.A., D.A., Design: H.K., M.Ş.P., N.Y., Data Collection or Processing: H.K., M.Ş.P., N.Y., Analysis or Interpretation: H.K., M.Ş.P., N.Y., Literature Search: H.K., Writing: H.K.

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