Received: 11 October 2021 | Revised: 19 November 2021 | Accepted: 8 December 2021

DOI: 10.1111/trf.16775

HEMAPHERESIS

TRANSFUSION

Safety and tolerability of solvent/detergent-treated plasma for pediatric patients requiring therapeutic plasma exchange: An open-label, multicenter, postmarketing study

Cassandra D. Josephson[1] | **Stuart Goldstein**[2] | **David Askenazi**[3] | **Claudia S. Cohn**[4] | **Philip C. Spinella**[5] | **Ara Metjian**[6] | **Ross M. Fasano**[1] | **Lejla Music-Aplenc**[7]

[1]Departments of Pathology and Laboratory Medicine and Pediatrics, Center for Transfusion and Cellular Therapies and Aflac Cancer and Blood Disorders Center, Emory University School of Medicine, Atlanta, Georgia, USA

[2]Cincinnati Children's, Cincinnati, Ohio, USA

[3]Children's of Alabama, University of Alabama at Birmingham, Birmingham, Alabama, USA

[4]University of Minnesota, Minneapolis, Minnesota, USA

[5]University of Pittsburg, Pittsburg, Pennsylvania, USA

[6]University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

[7]University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA

Correspondence
Cassandra D. Josephson, Department of Pathology, Emory University School of Medicine, 1405 Clifton Road, NE Atlanta, GA 30322, USA.
Email: cjoseph@emory.edu

Funding information
This study was sponsored and funded by Octapharma AG.

Abstract

Background: This study investigated the real-world safety and tolerability of solvent/detergent-treated (S/D) plasma for pediatric patients requiring therapeutic plasma exchange (TPE).

Study design and methods: LAS-213 was a multicenter, open-label, interventional, phase 4 study. Patients (≥2 to ≤20 years) receiving TPE therapy were eligible. A total plasma volume of 40–60 ml/kg was recommended, with an infusion rate not exceeding 0.020–0.025 citrate/kg body weight/min (<1 ml/kg body weight/min). The primary endpoint was assessment of safety, monitoring the following: serious adverse events (SAEs), adverse drug reactions (ADRs), thrombotic events (TEs), thromboembolic events (TEEs), and specific laboratory tests.

Results: In total, 41 children (2 to <12 years [$n = 15$]; 12 to <17 years [$n = 13$]; ≥17 years [$n = 13$]) underwent 102 TPEs with a total of 135,137 ml of S/D plasma exchanged. Each patient group received between 1 and 6 TPEs (mean: 2.5 TPEs). Actual dose administered per TPE was 4–72 ml/kg (mean: 28.6 ml/kg), with a mean total volume of 1324.9 ml (range: 113–4000 ml). Overall safety was excellent for 96/102 (94.0%) TPEs. Six TPEs had a "moderate" safety profile for four patients experiencing eight ADRs. Of these, seven were mild in intensity and one (pyrexia) was moderate, all resolving by study

end. Mild citrate toxicity ($n = 2$) was the most common ADR. One SAE was reported but was unrelated to the study drug. No TEs, TEEs, or changes in laboratory safety parameters were reported.

Conclusion: S/D plasma was well tolerated and demonstrated favorable safety, supporting the use of S/D plasma for TPE in pediatrics.

KEYWORDS

blood component preparations, hemostasis, pediatrics, plasma derivatives, transfusion practices

1 | INTRODUCTION

Therapeutic plasma exchange (TPE), or plasmapheresis, is an extracorporeal procedure in which plasma is removed from the blood and is replaced by infusion of an appropriate exogenous fluid, along with the return of the cellular blood components, to restore the patient's blood volume and function.[1] This process expunges the blood of disease-mediating components residing in the plasma, such as autoimmune antibodies, cryoglobulins, endotoxins, and cholesterol-containing lipoproteins.[2] As such, this treatment is frequently applied for the management of neurologic, hematologic, renal, and metabolic conditions.[1] TPE is performed for many of the same indications in pediatric patients as it is in adults; however, the current guidance is largely based on clinical experience in adults as limited data are available on the use of TPE in pediatric patients.[2–7]

Several plasma-based products are suitable as replacement fluids for TPE, such as fresh-frozen plasma (FFP), albumin, cryoprecipitate-poor plasma (CPP), and solvent/detergent-treated (S/D) plasma.[3,5,6,8] The use of S/D plasma confers several advantages.[9] For instance, while FFP is collected from a single donor, S/D plasma is produced from pooling multiple single-donor FFP units. Thus, FFP has significant variability in the levels of clotting factors, while S/D plasma has a standardized clotting factor content and lower variability in thrombin generation capacity, critical for effective hemostasis.[9–11] Viral inactivation is another benefit of S/D plasma. During the manufacturing process, plasma is treated to dissolve the lipid envelope surrounding viruses such as human immunodeficiency virus, hepatitis B and C, and Zika virus.[12,13] S/D plasma also undergoes an extensive plasma purification process, significantly lowering the number of residual platelets and microparticles. This process has been shown to reduce the risk of transfusion complications such as transfusion-related acute lung injury and allergic reactions.[14–17]

Octaplas™ (Octapharma AG, Switzerland) is an S/D plasma preparation of pooled ABO blood group-specific plasma that has undergone virus inactivation and purification.[18] Octaplas, a second-generation product also referred to as OctaplasLG (Octapharma AG, Switzerland), and henceforth referred to as S/D plasma, undergoes additional processing to eliminate prion proteins using affinity chromatography, reducing the transmission risk of prion diseases such as variant Creutzfeldt-Jakob disease. This product is approved in the United States for TPE in patients with thrombotic thrombocytopenic purpura (TTP), as well as for the replacement of multiple coagulation factors in patients with liver disease and patients undergoing cardiac surgery or liver transplantation.[17,18]

A previous pediatric postmarketing study (LAS-212) evaluated the use of S/D plasma in cardiac surgery and liver transplant patients aged 0–16 years.[17] In contrast, the purpose of this postmarketing study (LAS-213) was to investigate the safety and tolerability of S/D plasma for the management of pediatric patients who require TPE, where 1.0–1.5 plasma volumes of the product are infused at one time, for any TPE indication. This study aimed to obtain additional safety information relating to the use of S/D plasma in the clinical settings in children requiring TPE through assessment of adverse drug reactions (ADRs), serious adverse events (SAEs), thrombotic events (TEs), and thromboembolic events (TEEs).

2 | MATERIALS AND METHODS

2.1 | Study design

The LAS-213 study (NCT01938378) was an open-label, interventional, phase 4 study performed across seven pediatric hospital centers in the United States. Patients ≥2 to ≤20 years of age receiving treatment with S/D plasma for TPE one or more times between June 2015 and January 2019 were eligible for inclusion. Key exclusion criteria were patients with known homozygous congenital protein S deficiency; severe hypersensitivity reaction to plasma-derived products or to any excipients in S/D plasma; known immunoglobulin A deficiency;

TABLE 1 Schedule of assessments in the study

Time-points	Screening (≤14 days prior to first TPE)	1-week (7-day) study treatment period			Follow-up[a,b]
		Within 24 h before each TPE procedure	Study treatment (during each TPE procedure)	Between 30 min and 3 h after each TPE procedure	24 h after each TPE procedure
Obtain informed consent	X				
Review of inclusion/exclusion criteria	X				
Physical examination	X				
Medical history (including relevant current concomitant medications, and blood group type [ABO] recording)	X				
Demographics	X				
Vital signs (heart rate, respiratory rate, temperature, and blood pressure assessment)		X		X	
Blood draw CBC and Chem 7	X	X		X	
Blood draw for ionized calcium		X	X[c]		X
Record total volume of S/D plasma infused at each infusion episode			X		
Record the type of machine used for TPE (filtration or centrifugation)			X		
Record any SAEs, ADRs (including transfusion reactions), TEs, TEEs, and concomitant medication use			←----------Continuously----------→		
Pregnancy test for females of childbearing potential	X				
Investigator's overall assessment of safety[d]					X

Abbreviations: ADR, adverse drug reaction; CBC, complete blood count; SAE, serious adverse event; TE, thrombotic event; TEE, thromboembolic event; TPE, therapeutic plasma exchange.

[a]Follow-up procedures (ionized calcium sample and investigator's assessment) were performed 24 (±2) hours after the TPE concluded. Follow-up procedures may have been performed sooner if it was not practical to obtain these during the 24-hour post-TPE period. If it was not practical to obtain a blood sample for testing ionized calcium, the laboratory assessment could be skipped. If follow-up assessments were not performed, the reason was clearly documented (e.g., patient discharged prior to 24 h after the end of the last TPE).

[b]If plasma was needed for administration during the study follow-up period, S/D plasma was given. After the end of the follow-up, if plasma was needed, this was provided according to institutional standard of care.

[c]The first sample was drawn within 90 min after start of the TPE.

[d]Investigator's evaluation of overall safety was performed 24 (±2) hours after each TPE procedure.

pregnancy; or use of angiotensin-converting enzyme inhibitors within 72 h of the first infusion or during the study. Parental consent (and assent from older children/adolescents) was obtained during the 14-day screening period. For each patient, there was a maximum 7-day treatment period in which one or more TPE procedures took place, with a 24-hour follow-up after each TPE procedure.

The recommended dose of total plasma volume was 40 to 60 ml/kg, at the discretion of the treating physician. The dosing regimen was modified depending on the therapeutic treatment plan and the investigator's evaluation of the patient's clinical situation. The infusion rate was not to exceed 0.020 to 0.025 citrate/kg body weight/min, equivalent to less than 1 ml/kg body weight/min.

2.2 | Study endpoints

The primary endpoint encompassed monitoring the following in at least 40 patients: SAEs, ADRs, TEs, and TEEs caused by the S/D plasma, which was used for plasma exchange during the 7-day study period.

Secondary endpoints included the assessment of abnormalities in laboratory parameters, including complete blood count (CBC), Chem 7 laboratory panel, and ionized calcium levels, as well as the investigator's assessment of the overall safety of S/D plasma in this setting.

2.3 | Safety assessments

The severity of all ADRs was graded. The three categories were defined as follows: mild—ADR usually transient, which caused discomfort but did not interfere with the patient's routine activities; moderate—ADR, which was sufficiently discomforting to interfere with the patient's routine activities; severe—ADR, which was incapacitating and prevented the pursuit of the patient's routine activities.

An Independent Data Monitoring Committee (IDMC) monitored safety data and was composed of recognized experts in the fields of anesthesiology, pediatrics, and oncology who were not actively recruiting patients.

Twenty-four hours prior to each TPE procedure, vital signs were assessed, and blood was drawn for laboratory safety assessments including CBC, Chem 7, and ionized calcium to assess for citrate toxicity, defined as a fall in ionized calcium based on the investigator's interpretation. Blood draw for ionized calcium was also performed during treatment, with the first sample taken within 90 minutes after the start of TPE. Between 30 minutes and 3 h after TPE, vital signs were reassessed, and blood was drawn for CBC and Chem 7. At 24 h post TPE, blood was drawn for a final measurement of ionized calcium, if practical. The schedule of study assessments is shown in Table 1.

Safety was rated by the investigator 24 h after each TPE according to the predefined category which best described the patient's experience of study treatment. The three categories were defined as follows: excellent—treatment was well tolerated by the patient; moderate—ADR(s) were observed, but easily resolved or not clinically significant; and poor—ADR(s) were observed requiring significant medical intervention.

2.4 | Statistical analysis

All data collected were summarized and presented descriptively to facilitate review of population homogeneity and assess general patterns within and between the specific age subgroups. Data presented are for the safety population, which consisted of all patients who received at least one infusion of S/D plasma. Continuous variables are reported as mean (standard deviation) and range. Categorical variables are reported as number and percentage. The rates of SAEs, ADRs, TEs, and TEEs were calculated and presented, together with the associated 95% confidence intervals, per age group and in total. No confirmatory hypothesis testing was planned. Any confidence interval presented is to be understood in the exploratory sense. Statistical analyses were performed using SAS software version 9.4.

3 | RESULTS

3.1 | Demographics

Forty-one patients aged ≥2 to ≤20 years were screened and enrolled into the study. Table 2 describes the demographics for the three groups: Group 1, aged 2 to <12 years; Group 2, aged 12 to <17 years; and Group 3, aged ≥17 years. The most common underlying disease categories reported overall were immune system disorders (in 34.1% of patients) followed by nervous system disorders (in 29.3% of patients). A higher proportion of patients aged 2 to 12 years had a diagnosis of nervous system disorders (60.0%) than patients aged 12 to <17 years or ≥17 years (15.4% and 7.7%, respectively). A higher proportion of patients aged 12 to <17 years or ≥17 years had initial diagnoses of immune system disorders (38.5% and 53.8%, respectively) and renal disorders (30.8% in each age group) in comparison with the 2 to <12 years age group.

Physical examination revealed more clinically significant abnormal findings for patients aged 2 to <12 years ($n = 9$) than any other cohort (aged 12 to <17 years: $n = 3$; aged ≥17 years: $n = 1$), with neurologic ($n = 3$); respiratory ($n = 3$); cardiovascular ($n = 1$); head, eyes, ears, nose, and throat ($n = 1$); and musculoskeletal ($n = 1$) findings being reported. The most frequently reported past diseases by preferred term were heart transplant and renal transplant (each in 22.0% of patients overall) and nephrectomy (in 19.5% of patients). All patients had ongoing concomitant diseases at screening, the most common of which were renal and urinary disorders (in 46.3% of patients) and vascular disorders (in 41.5% of patients).

3.2 | Dosing

In total, 102 TPEs were performed resulting in a total of 135,137 ml of S/D plasma administered across the 41 patients in the study. Centrifugal TPE was used for 38 patients (92.7%), while membrane filtration TPE was used for three patients (7.3%). Most patients (36/41) received S/D plasma specific to their blood group. In

TABLE 2 Demographic data

Parameter	Age Group 1 (2–<12 years) *N* = 15	Age Group 2 (12–<17 years) *N* = 13	Age Group 3 (≥17 years) *N* = 13	All patients *N* = 41
Age (years)				
Mean (SD)	6.1 (2.34)	13.8 (1.52)	18.1 (1.04)	12.3 (5.40)
Range	2–10	12–16	17–20	2–20
Sex (*n*, [%])				
Male	3 (20.0)	6 (46.2)	9 (69.2)	18 (43.9)
Female	12 (80.0)	7 (53.8)	4 (30.8)	23 (56.1)
Race (*n*, [%])				
White	13 (86.7)	9 (69.2)	10 (76.9)	32 (78.0)
Black or African American	2 (13.3)	2 (15.4)	3 (23.1)	7 (17.1)
American Indian or Alaska Native	0 (0.0)	2 (15.4)	0 (0.0)	2 (4.9)
Weight (kg)				
Mean (SD)	27.0 (12.2)	61.4 (23.4)	70.5 (18.29)	51.7 (26.41)
Range	15–61	39–124	40–101	15–124
Diagnosis (*N*, [%])				
Immune system disorders	2 (13.3)	5 (38.5)	7 (53.8)	14 (34.1)
Heart transplant rejection	2 (13.3)	2 (15.4)	5 (38.5)	9 (12.2)
Kidney transplant rejection	0 (0.0)	3 (23.1)	1 (7.7)	4 (9.8)
ANCA vasculitis	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Infections and infestations	3 (20.0)	1 (7.7)	0 (0.0)	4 (9.8)
Septic shock	1 (6.7)	1 (7.7)	0 (0.0)	2 (4.9)
Streptococcal toxic shock syndrome	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Myelitis	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Nervous system disorders	9 (60.0)	2 (15.4)	1 (7.7)	12 (29.3)
Myasthenia gravis	0 (0.0)	1 (7.7)	1 (7.7)	2 (4.9)
Autoimmune encephalitis	3 (20.0)	0 (0.0)	0 (0.0)	3 (7.3)
Acute transverse myelitis	2 (13.3)	0 (0.0)	0 (0.0)	2 (4.9)
Encephalitis lethargica	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.4)
CNS tumefactive demyelinating syndrome	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Antimyelin oligodendrocyte glycoprotein demyelinating disease of CNS	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Optic neuritis	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Acute flaccid myelitis	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)
Renal and urinary disorders	0 (0.0)	4 (30.8)	4 (30.8)	8 (19.5)
Focal segmental glomerulosclerosis/renal treatment	0 (0.0)	4 (30.8)	3 (23.1)	7(17.1)
Antibody mediated rejection in renal graft	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Other	1 (6.7)	1 (7.7)	1 (7.7)	3 (7.3)
Vasculitis	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.4)
Macrophage activation syndrome	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Thrombotic Microangiopathy anemia	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)

TABLE 2 (Continued)

Parameter	Age Group 1 (2–<12 years) $N = 15$	Age Group 2 (12–<17 years) $N = 13$	Age Group 3 (≥17 years) $N = 13$	All patients $N = 41$
ABO blood group (n, [%])				
A	5 (33.3)	6 (46.2)	3 (23.1)	14 (34.1)
B	4 (26.7)	1 (7.7)	4 (30.8)	9 (22.0)
AB	1 (6.7)	0 (0.0)	1 (7.7)	2 (4.9)
O	5 (33.3)	6 (46.2)	5 (38.5)	16 (39.0)

Abbreviations: ANCA, antineutrophil cytoplasm antibodies; CNS, central nervous system; SD, standard deviation.

TABLE 3 Exposure to study drug per patient

	Age Group 1 (2–<12 years) $N = 15$	Age Group 2 (12–<17 years) $N = 13$	Age Group 3 (≥17 years) $N = 13$	All patients $N = 41$
Number of TPEs				
Mean (SD)	2.5 (1.36)	2.5 (1.81)	2.5 (1.45)	2.5 (1.50)
Range	1–5	1–6	1–5	1–6
Volume of study drug administered (ml)				
Mean (SD)	1750.9 (2241.58)	4838.1 (3602.27)	3536.8 (2779.04)	3296.0 (3107.31)
Range	200–7937	600–11,891	500–9220	200–11,891
Actual dose (ml/kg)				
Mean (SD)	67.4 (78.67)	96.8 (89.99)	49.9 (37.82)	71.2 (73.43)
Range	4–275	10–283	7–135	4–283
Infusion rate (ml/kg/min)				
Mean (SD)	0.41 (0.130)	0.37 (0.094)	0.32 (0.057)	0.37 (0.106)
Range	0.2–0.7	0.3–0.5	0.2–0.4	0.2–0.7

Abbreviations: SD, standard deviation; TPE, therapeutic plasma exchange.

urgent cases or where the specific blood group was not available, patients were administered nonblood group-specific universal AB S/D plasma. Five patients received universal AB S/D plasma: two patients of blood group O, two of blood group A, and one of blood group B.

Each patient underwent between one and six TPEs, with a mean of 2.5 TPEs overall and in each age group (Tables 3 and S1). The actual dose administered to patients per TPE ranged from 4 ml/kg to 72 ml/kg (mean: 28.6 ml/kg), with a mean total volume administered per TPE of 1324.9 ml (range: 113–4000 ml). Mean infusion rates were similar between age groups (range: 0.32–0.41 ml/kg/min).

3.3 | Safety

Overall safety, assessed by investigators 24 h after each TPE, was reported as excellent for 96 out of 102 TPEs (94.0%) (Figure 1). A total of eight ADRs occurred in four patients, of which seven were mild in intensity and were recovered/resolved by the end of the study (Table 4). One ADR (pyrexia) was moderate in intensity; this resolved by the end of the study. For the four patients who experienced ADRs, overall safety was assessed as "moderate" for six TPEs, per the prespecified definition.

The most frequently reported ADR was mild citrate toxicity ($n = 2$), with both events reported for Group 2 (12 to <17 years). Other ADRs, each reported in one patient, comprised headache, increased inflammatory markers, myalgia, nausea, pyrexia, and urticaria. No TEs or TEEs were reported by the investigators or IDMC. One SAE, multiple organ failure secondary to sepsis, was reported and led to the one death in the study. This SAE occurred in a patient with high-risk B-cell acute lymphoblastic leukemia who was receiving TPE to treat septic shock. The investigator considered this event as unrelated to the study drug.

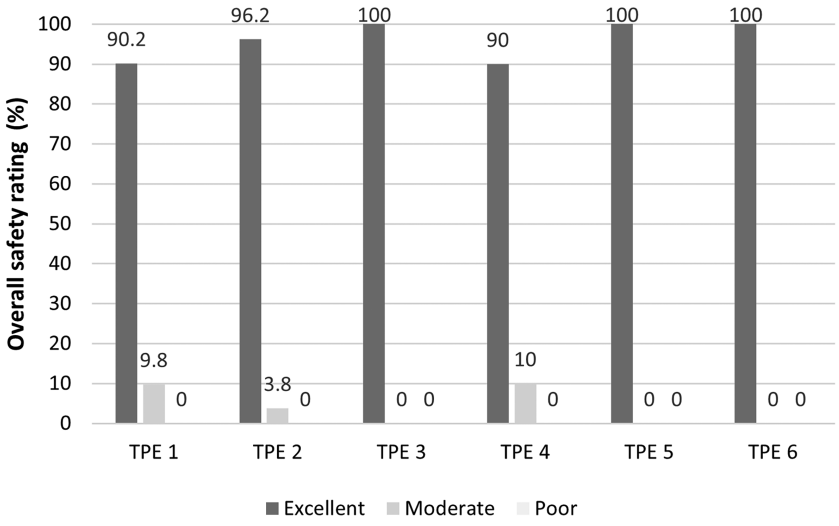

FIGURE 1 Investigators' assessments of overall safety per TPE with S/D plasma. Patients received between 1 and 6 TPEs with a mean of 2.5 TPEs ($N = 41$). Percentages are calculated on the number of patients with non-missing data for the specific TPE. Excellent: defined as the treatment was well tolerated by the patient; moderate: defined as ADR(s) were observed, but easily resolved or not clinically significant; poor: defined as ADR(s) were observed requiring significant medical intervention. ADR, adverse drug event; S/D plasma, solvent/detergent-treated plasma; TPE, therapeutic plasma exchange

TABLE 4 Summary of safety events

	Age Group 1 (2–<12 years) $N = 15$	Age Group 2 (12–<17 years) $N = 13$	Age Group 3 (≥17 years) $N = 13$	All patients $N = 41$
Number (%) of ADRs	0 (0.0)	5 (38.5)	3 (23.1)	8 (19.5)[a]
Citrate toxicity	0 (0.0)	2 (15.4)	0 (0.0)	2 (4.9)
Headache	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.4)
Pyrexia	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.4)
Urticaria	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.4)
Inflammatory marker increased	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Myalgia	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Nausea	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.4)
Number (%) of SAEs	1 (6.7)	0 (0.0)	0 (0.0)	1 (2.4)[b]
Number (%) of TEs or TEEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of ADRs, SAEs, TEs, and TEEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ADR, adverse drug reaction; SAE, serious adverse event; TE, thrombotic event; TEE, thromboembolic event.
[a]All were mild in severity except pyrexia (moderate).
[b]Assessed as unrelated to treatment.

There were no marked changes in the laboratory results from pre- to post TPE. Most parameters were considered normal or abnormal but not clinically significant. Transient abnormal changes observed for creatinine, blood urea nitrogen, potassium, glucose, and white blood cells were regarded as clinically significant (Tables S2 and S3). However, these results were not related to the study drug and were not unexpected for the patient population. Ionized calcium levels remained relatively stable from pre- to post TPE and at the 24-hour post-TPE follow-up visits. There were three abnormal ionized calcium values reported by the investigators during the study, one of which was related to study drug and reported as an ADR.

There were no clinically meaningful shifts in vital signs, with minimal fluctuations observed in blood pressure, heart rate, respiratory rate, and body temperature for individual TPE infusions. There were also no clinically meaningful shifts observed in any of these measurements from pre- to post TPE.

4 | DISCUSSION

This postmarketing study investigated the safety and tolerability of S/D plasma in the management of pediatric patients requiring TPE. S/D plasma exhibited a favorable safety profile and was well tolerated in 41 pediatric

patients undergoing a total of 102 TPE procedures in routine clinical practice. The overall safety of S/D plasma for TPE as assessed by the investigators was rated as "excellent" for more than 90% of patients 24 h after each TPE. Four patients experienced a total of eight ADRs, 7/8 (87.5%) of which were mild in severity and were easily resolved or deemed not clinically significant; the one moderate ADR (pyrexia) also resolved by study end. The most common ADR was mild citrate toxicity, well known to be associated with TPE; as such, all but one patient received concomitant calcium medications as prophylaxis or as standard of care, with additional intravenous calcium being administered to resolve the two cases of citrate toxicity.[8] The overall safety was assessed by the investigators as "moderate" for the four patients who experienced ADRs. One SAE, which was fatal, was reported and was classified as unrelated to the study drug. Importantly, no TEs or TEEs were observed by the investigators or IDMC. Five patients received nonblood group-specific universal AB S/D plasma, without complications. Taken together, these results add to the body of data supporting the use of S/D plasma for pediatric patients undergoing TPE.

Several studies already attest to the safety and efficacy of S/D plasma for TPE for adult patients.[8,19,20] Scully et al[8] retrospectively reviewed 50 successive episodes of TTP requiring TPE with S/D plasma. Here, citrate toxicity was also reported for TPE patients, despite the administration of intravenous calcium; however, the number of citrate reactions was significantly lower for patients receiving S/D plasma (6.9%) in comparison to patients receiving CPP (18%) ($p < 0.0001$). Moreover, plasma-associated allergic reactions were also significantly reduced for patients receiving S/D plasma.[8] Both S/D plasma and CPP were shown to be equally efficacious, and there was no documented viral transmission with either product. Another study, by Edel et al,[19] examined the use of S/D plasma for TPE in eight high-use patients requiring recurrent therapy (500 treatments). S/D plasma was well tolerated, with no ADRs or major complications being reported.[19]

More recent studies have also shown S/D plasma products to have a favorable safety profile for pediatric patients.[3,17,21] For instance, Witt et al[3] examined the use of nonspecified S/D plasma for 324 TPE treatments in 35 pediatric patients. Patients received either S/D plasma alone, human albumin, or a combination of S/D plasma and human albumin. S/D plasma was demonstrated to preserve hemostatic parameters in this pediatric population, with no apparent safety concerns.[3] Of note, TPE was used in a wide range of pediatric patients, some as young as 1-year old.[3]

Guidelines recommend the use of S/D plasma products over other replacement fluids for TPE in TTP for pediatric patients.[22–24] In some countries, such as Norway and Finland, there is no FFP available; therefore, S/D plasma products are the sole plasma derivatives for TPE.[25,26] In 2006, the UK Department of Health declared S/D plasma products the preferred plasma choice for high-volume users, including patients needing TPE, because of the rigorous viral inactivation protocol performed during manufacture.[4,27] The use of S/D plasma products has also been shown to be associated with a lower risk of allergic reactions compared with whole blood-derived and apheresis-derived plasma.[15]

Data from the present study contribute to the growing body of evidence supporting the use of S/D plasma for TPE for pediatric patients. This study was unable to evaluate the efficacy of this approach due to the small sample size. This limitation was not unexpected for the patient population and has been reported elsewhere.[3] Moreover, this postmarketing study had no comparator arm to assess safety and tolerability in comparison with other treatment options currently used for TPE. Of note, passive surveillance was used for monitoring TEs or TEEs. Nonetheless, this study successfully generated additional safety data on the use of S/D plasma in real-world settings, with no TEs, TEEs, or related SAEs observed in pediatric patients receiving S/D plasma for TPE.

In conclusion, in this postmarketing study, S/D plasma demonstrated a favorable safety profile and was well tolerated for pediatric patients requiring TPE. The results, together with those of previous studies of S/D plasma, support the use of this S/D plasma in this patient population.

ACKNOWLEDGMENT

Editorial assistance was provided by Portland Medical Communications Ltd and was funded by Octapharma AG. Dr. Susan Goobie: Senior Associate in Perioperative Anesthesia, Associate Professor of Anaesthesia (Boston Children's Hospital); Dr. Swayamprabha Sadanandan: Associate Chairman of the Department of Pediatrics, Division chief of Pediatric Hematology Oncology emeritus (Brooklyn Hospital Center); Dr. Peter J Davis: Anesthesiologist-in-Chief for Transplant Anesthesia (Children's Hospital of Pittsburgh of UPMC), all served on the IDMC.

CONFLICT OF INTEREST

CDJ is an associate editor for Transfusion, consultant for Octapharma, Immucor, Cellphine, and has an unrestricted grant with Medtronics. SG, DA, CSC, PCS, AM, RF, and LMA have no conflicts of interest.

ORCID

Cassandra D. Josephson https://orcid.org/0000-0003-2543-991X
Claudia S. Cohn https://orcid.org/0000-0001-9847-0470
Philip C. Spinella https://orcid.org/0000-0003-1721-0541
Ross M. Fasano https://orcid.org/0000-0001-8692-4041

REFERENCES

1. Fernández-Zarzoso M, Gómez-Seguí I, de la Rubia J. Therapeutic plasma exchange: review of current indications. Transfus Apher Sci. 2019;58(3):247–53.
2. Schmidt JJ, Asper F, Einecke G, Eden G, Hafer C, Kielstein JT. Therapeutic plasma exchange in a tertiary care center: 185 patients undergoing 912 treatments-a one-year retrospective analysis. BMC Nephrol. 2018;19(1):12.
3. Witt V, Pichler H, Beiglboeck E, Kursten F, Weidner L. Changes in hemostasis caused by different replacement fluids and outcome in therapeutic plasma exchange in pediatric patients in a retrospective single center study. Transfus Apher Sci. 2017;56(1):59–65.
4. McGuckin S, Westwood JP, Webster H, Collier D, Leverett D, Scully M. Characterization of the complications associated with plasma exchange for thrombotic thrombocytopaenic purpura and related thrombotic microangiopathic anaemias: a single institution experience. Vox Sang. 2014;106(2):161–6.
5. Joseph C, Siddiqui S, Shah S, Solomon CH, Srivaths PR. Therapeutic plasma exchange: single-center experience in children with kidney disorders. Pediatr Nephrol. 2021;36(3):621–9.
6. Altuntas F, Aydogdu I, Kabukcu S, Kocyigit I, Cıkım K, Sarı I, et al. Therapeutic plasma exchange for the treatment of thrombotic thrombocytopenic purpura: a retrospective multicenter study. Transfus Apher Sci. 2007;36(1):57–67.
7. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the writing Committee of the American Society for apheresis: the eighth special issue. J Clin Apher. 2019;34(3):171–354.
8. Scully M, Longair I, Flynn M, Berryman J, Machin SJ. Cryosupernatant and solvent detergent fresh-frozen plasma (Octaplas) usage at a single Centre in acute thrombotic thrombocytopenic purpura. Vox Sang. 2007;93(2):154–8.
9. Spinella PC, Frazier E, Pidcoke HF, Dietzen DJ, Pati S, Gorkun O, et al. All plasma products are not created equal: characterizing differences between plasma products. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S18–25.
10. Heger A, Römisch J, Svae TE. A biochemical comparison of a pharmaceutically licensed coagulation active plasma (Octaplas) with a universally applicable development product (Uniplas) and single-donor FFPs subjected to methylene-blue dye and white-light treatment. Transfus Apher Sci. 2006;35(3):223–33.
11. Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth. 2011;106(4):505–11.
12. Horowitz B, Bonomo R, Prince AM, Chin SN, Brotman B, Shulman RW. Solvent/detergent-treated plasma: a virus-inactivated substitute for fresh frozen plasma. Blood. 1992;79(3):826–31.
13. Kuhnel D, Muller S, Pichotta A, et al. Inactivation of Zika virus by solvent/detergent treatment of human plasma and other plasma-derived products and pasteurization of human serum albumin. Transfusion. 2017;57(3pt2):802–10.
14. Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion. 2009;49(3):440–52.
15. Saadah NH, van der Bom JG, Wiersum-Osselton JC, Richardson C, Middelburg RA, Politis C, et al. Comparing transfusion reaction risks for various plasma products - an analysis of 7 years of ISTARE haemovigilance data. Br J Haematol. 2018;180(5):727–34.
16. Saadah NH, van Hout FMA, Schipperus MR, le Cessie S, Middelburg RA, Wiersum-Osselton JC, et al. Comparing transfusion reaction rates for various plasma types: a systematic review and meta-analysis/regression. Transfusion. 2017;57(9):2104–14.
17. Spinella PC, Borasino S, Alten J. Solvent/detergent-treated plasma in the Management of Pediatric Patients who Require Replacement of multiple coagulation factors: an open-label, multicenter, post-marketing study. Front Pediatr. 2020;8:572.
18. Octapharma. Octaplas prescribing information. https://www.octaplasus.com/wp-content/uploads/2021/03/20210202_pil_952_US_25.pdf (2021). Accessed 24 Jun.
19. Edel E, Al-Ali HK, Seeger S, et al. Efficacy and safety profile of solvent/detergent plasma in the treatment of acute thrombotic thrombocytopenic Purpura: a single-center experience. Transfus Med Hemother. 2010;37(1):13–9.
20. Liumbruno GM, Franchini M. Solvent/detergent plasma: pharmaceutical characteristics and clinical experience. J Thromb Thrombolysis. 2015;39:118–28.
21. Camazine MN, Karam O, Colvin R, Leteurtre S, Demaret P, Tucci M, et al. Outcomes related to the use of frozen plasma or pooled solvent/detergent-treated plasma in critically ill children. Pediatr Crit Care Med. 2017;18:e215–23.
22. Howell C, Douglas K, Cho G, el-Ghariani K, Taylor P, Potok D, et al. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. British Committee for Standards in Haematology. Transfus Med. 2015;25(2):57–78.
23. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158(3):323–35.
24. New HV, Berryman J, Bolton-Maggs PH, et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol. 2016;175(5):784–828.
25. Krusius T, Auvinen M-K, Nikkinen L. Introduction of Octaplas in clinical use decreased the rate of severe adverse reactions. Vox Sang. 2009;96(Suppl 1):1–62.
26. Frønsdal KB, Knoph Kvamme M, Stoinska-Schneider A, et al. NIPH systematic reviews: executive summaries. Alternatives of plasma for transfusion to patients. Oslo, Norway: Knowledge

Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2015.
27. Taylor, C, Cohen, H, Jones, H, et al. Serious hazards of transfusion (SHOT), Annual Report 2007. https://www.shotuk.org/wp-content/uploads/myimages/2010/03/SHOT-Report-2007.pdf (2007). Accessed 17 Mar, 2021.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Josephson CD, Goldstein S, Askenazi D, Cohn CS, Spinella PC, Metjian A, et al. Safety and tolerability of solvent/detergent-treated plasma for pediatric patients requiring therapeutic plasma exchange: An open-label, multicenter, postmarketing study. Transfusion. 2022;62:396–405. https://doi.org/10.1111/trf.16775