European Review for Medical and Pharmacological Sciences 2014; 18: 3696-3701

Beneficial therapeutic effects of hemoperfusion in the treatment of severe Stevens-Johnson syndrome/toxic epidermal necrolysis: preliminary results

Y.-M. WANG[1,2], Y.-H. TAO[1], T. FENG[2], H. LI[2]

[1]Department of Pediatrics, West China Second University Hospital, Sichuan University, Sichuan, China
[2]Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases and Birth Defects of Ministry Education, West China Second University Hospital, Sichuan University, Sichuan, China

Abstract. – OBJECTIVE: Most of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe drug eruptions. There is currently no established treatment due to a lack of controlled/blinded studies. High-dose glucocorticoids and intravenous immunoglobulins (IVIG) therapy have been widely used, but these approaches remain controversial. This study introduces a novel method by which to treat severe SJS/TEN patients who were refractory to glucocorticoids and IVIG.

PATIENTS AND METHODS: Seven patients with SJS and three patients with TEN were enrolled in this non-blinded, uncontrolled study. The average patient age was 8.1 years. The male to female ratio was 1:1. Hemoperfusion was conducted daily using a HA280 resin sorbent column until new skin lesions ceased appearing and the skin started healing with visible re-epithelialization.

RESULTS: The average BSA involvement in SJS and TEN was 8.57% and 75%, respectively. The number of hemoperfusion sessions ranged from 3 to 5. Hemoperfusion led to prompt improvements in general health and halted the disease progression. All children were discharged and recovered completely. The average length of stay was 14.4 days. Four patients experienced adverse reactions: femoral vein thrombosis (N = 2), hypotension (N = 1), and cardiac palpitation (N = 1).

CONCLUSIONS: Hemoperfusion may be a useful adjunct treatment for patients with severe SJS/TEN if the initial treatment with glucocorticoids and IVIG fails.

Key Words:
Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug eruption, Hemoperfusion, Treatment, Children.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, life-threatening, mucocutaneous diseases. Most of SJS/TEN are severe drug eruptions. The diseases are characterized by epidermal necrosis with detachment, erosion of the mucous membranes, and severe constitutional symptoms[1,2]. Because SJS and TEN are rare and occur unpredictably, it is impossible to conduct controlled/blinded studies. Evidence-based studies or generally accepted guidelines are currently unavailable, and no optimal treatment has been established[3,4]. The basic treatment is the immediate withdrawal of all potentially responsible drugs. The principal clinical approaches include local management, fluid replacement, nutritional support, and systemic treatments. For systemic treatments, high-dose glucocorticoids and intravenous immunoglobulins (IVIG) therapy have been widely used. However, the use of this therapy is controversial[5-7].

Hemoperfusion is an extracorporeal blood purification treatment that is based on adsorption and has been applied in many non-renal diseases. The aim of this study was to investigate the therapeutic effects of hemoperfusion in SJS/TEN patients who were refractory to glucocorticoids and IVIG.

Patients and Methods

Study Design

Because SJS and TEN are rare and occur unpredictably, we performed a non-blinded, uncontrolled study of children hospitalized with severe SJS or TEN at the West China Second University Hospital, Sichuan University, China. The study was approved by the Ethical Review Board of Investigation in Human Beings of the West China Second University Hospital, Sichuan University.

Corresponding Author: Yuhong Tao, MD; e-mail: hxtyh@sina.com

Patients

Hospitalized children with SJS or TEN in the West China Second University Hospital were selected for hemoperfusion on a patient-by-patient basis by the treating pediatrician. SJS and TEN were diagnosed according to the standard textbooks and literature[8]. SJS was diagnosed according to the following criteria: (1) atypical target-like lesions, (2) a positive Nikolsky sign, (3) involvement of at least two mucous membranes, (4) fever, and (5) histology compatible with SJS. The diagnostic criteria for TEN included: (1) bullae or erosions covering ≥ 30% of the total body surface area (BSA) or involving three separate anatomical regions, (2) bullae developing on an erythematous base, (3) lesions occurring on non-sun-exposed skin, (4) peeling of skin areas >300 mm^2, (5) frequent involvement of mucous membranes, (6) appearance of tenderness within 48 hours of the onset of the rash, (7) a positive Nikolsky sign, (8) fever, and (9) histology compatible with drug-induced TEN. From June 2008 to January 2014, ten children with SJS or TEN were eligible for this study. All parents of the patients of the patients gave informed consent. Consecutive treatment with intravenous methylprednisolone (10-30 mg/kg, qd, 3 days) and IVIG (1 g/kg, qd, 2 days) therapy was ineffective in these patients. Patient information was recorded, including age and gender, as well as the implicated drug, extent of eruption (% BSA), and number of mucous membranes involved upon hospital admission.

Medical Treatment

In all cases, the suspected drugs were discontinued. Full-dose prednisone (1.5-2.0 mg/kg daily) was administered together with hemoperfusion to all patients until the dermal manifestations were controlled (i.e., decreased redness, scabbing blisters, no new eruptions).Then, the prednisone dose was gradually decreased. For patients with liver or kidney injuries, agents such as vitamin C and inosine were administered for hepatic or renal protection. Measures for preventing secondary skin infections were also administered.

Hemoperfusion

Hemoperfusion was performed daily until new skin lesions stopped appearing and the skin started to heal with visible re-epithelialization. Before each hemoperfusion session, a complete blood cell count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and ionized calcium were measured for each patient. Vascular access was established by inserting an indwelling double-lumen catheter into the femoral vein. A HA280 resin sorbent column (Zhuhai Lizhu Biomedical Materials Co., Ltd., Zhuhai, Guangdong Province, China) was used. Unfractionated heparin was administered for anticoagulation (initial bolus dose = 1 mg/kg; 8-10 mg every 30 minutes). Heparin was stopped 0.5 hours prior to ending hemoperfusion, which was conducted once daily at a blood flow rate of 130-200 mL/min for 1.5-2 hours. During the treatment, systemic symptoms, body temperature, blood pressure, skin lesions, changes in laboratory data, and adverse reactions to hemoperfusion were monitored. The following information was recorded: the number of hemoperfusion sessions, treatment effect, length of stay, and complications resulting from hemoperfusion.

Results

Pre-Hemoperfusion Patient Characteristics

As shown in Table I, ten hospitalized children with severe SJS or TEN were enrolled in this study (male = 5; female = 5; mean age, 8.1 years; range, 2-13 years). Seven patients were diagnosed with SJS, and three patients were diagnosed with TEN. In five patients, the suspected drugs were antibiotics (i.e., cefaclor, cefixime, cefamox, cefotaxime sodium and amoxicillin; N=1 each). In the other five patients, the suspected drugs included antiepileptic drugs (phenobarbital sodium, N=2; sodium valproate, N=1; oxcarbazepine, N=1; and lamotrigine, N=1). The average BSA involvement was 8.57% in SJS and 75% in TEN. All patients had mucous membrane involvement (median, 2; range, 2 to 4 oral mucosa, conjunctiva, urothelium and anal). Fever was evident in nine patients. Eight patients presented with fevers ranging between 39 and 40.4°C, and 1 patient had a fever of 38°C. In five patients, drug-induced hepatitis was observed (i.e., alanine aminotransferase 98-668 IU/L, aspartate aminotransferase 93-411 IU/L, total bilirubin 50-177.8 mol/L and direct bilirubin 44-122.8 mol/L). Two patients with drug-induced kidney injuries presented with proteinuria.

Hemoperfusion Treatment Outcomes

As shown in Table I, six patients underwent three hemoperfusion sessions each. The other

Table I. Clinical profile of patients with severe SJS/TEN.

Patient No.	Age (years)	Gender	Diagnosis	Implicated drug	% body surface area	Number of mucous membrane involved	Abnormal liver function	Number of hemoperfusion sessions	Length of stay (days)	Complication of hemoperfusion
1	2	Male	SJS	Phenobarbital sodium	9%	2	Yes	3	36	Femoral vein thrombosis
2	5	Female	TEN	Cefaclor	80%	3	No	3	20	Femoral vein thrombosis
3	8	Male	SJS	Sodium valproate	8%	2	No	3	5	Hypotension
4	11	Female	TEN	Cefotaxime sodium	75%	3	No	3	15	No
5	13	Female	TEN	Cefamox	70%	4	Yes	3	14	Palpitations
6	10	Male	SJS	Oxcarbazepine	9%	2	Yes	5	8	No
7	12	Male	SJS	Lamotrigine	8%	2	Yes	5	11	No
8	5	Female	SJS	Phenobarbital sodium	9%	2	Yes	3	7	No
9	11	Male	SJS	Cefixime	9%	2	No	5	10	No
10	4	Female	SJS	Amoxicillin	8%	2	No	5	18	No

four patients underwent five hemoperfusion sessions each. Hemoperfusion led to a prompt improvement in general health and halted the disease progression. After one hemoperfusion session, the systemic symptoms of all patients were alleviated. Febrile patients became afebrile after one hemoperfusion sessions (N=7): three sessions were required for one patient, and four sessions were required for one patient. After one hemoperfusion session, nine children had significantly reduced rashes, and no new rashes appeared. In one patient, the rash persisted after five sessions of hemoperfusion and subsided after administering full-dose prednisone for one week. The drug-induced rashes disappeared after 8.2 days (on average) (3-21 days). After one hemoperfusion session, the fluid leakage/mucosal exudation was reduced. For all patients, the wounds were healed in seven days. After drug-induced hepatitis, liver function improved one week (N=3), ten days (N=1), or three weeks (N=1) after hemoperfusion cessation. After two hemoperfusion sessions, two children with proteinuria tested normal. All patients were eventually discharged. The average length of stay was 14.4 days (5-36 days).

Adverse Reactions to Hemoperfusion

Adverse reactions to hemoperfusion occurred in four patients, but thrombocytopenia, hypocalcaemia, and hypoglycemia were not observed. During hemoperfusion, one SJS patient had hypotension, and one TEN patient experienced palpitations. In these two patients, reducing the blood flow rate normalized the blood pressure, and the palpitations ceased. One day after hemoperfusion ceased, all patients underwent color Doppler ultrasonography. Femoral vein thrombosis was found in one TEN patient (length, 3 cm) and in one SJS patient (length, 12 cm). Thus, urokinase was administered (4,400 IU/kg daily), along with low molecular weight (LMW) heparin (60-80 IU/kg daily) and LMW dextran (10 mL/kg daily). After one week of treatment, another color Doppler ultrasonography revealed no femoral vein thrombosis.

Follow-up

All patients were followed for at least six months and recovered completely. To date, no patient has relapsed.

Discussion

SJS and TEN can be recognized as delayed cutaneous immune reactions. The reactions are elicited by cytotoxic T lymphocytes[9], natural killer cells[10], and dendritic cells[11]. In addition, various pro-inflammatory cytokines are present in the blister fluids, peripheral mononuclear cells and plasma of SJS/TEN patients[12-15]. The extent of the immune reaction is correlated with the severity of the drug eruption and tissue and organ damage[16]. The above data provide the rational for immunomodulating therapies to treat patients with SJS/TEN[9]. Because inflammation occurs through an interconnected network, drugs targeting a specific inflammatory mediator cannot fully inhibit the entire inflammatory response. Therefore, the curative effect is poor in some patients. The EuroSCAR study concluded that there was no sufficient evidence to support the superior effectiveness of glucocorticoids or IVIG therapy over supportive care for SJS/TEN[17].

Recent reviews have suggested that blood purification therapy could be used to treat patients with SJS/TEN in uncontrolled studies[5,16.] Hemoperfusion is a blood purification technique in which a sorbent is placed in direct contact with the blood in an extracorporeal circuit. Nonspecific adsorbents, typically charcoal and resins, attract solutes through a variety of forces, including hydrophobic interactions, ionic (or electrostatic) attraction, hydrogen bonding, and van der Waals interactions. Previous studies have indicated that hemoperfusion can improve the outcomes of many non-renal diseases, such as acute pancreatitis[18], Henoch-Schonlein purpura[19], sepsis [20], and acute lung injury[21]. The HA280 resin is a neutral microporous resin and being newly developed for use in China[19]. This resin specifically absorbs various medium-sized factors, including most pro-inflammatory cytokines. In our study, none of the ten patients responded to methylprednisolone or high-dose IVIG treatments, and their clinical statuses quickly deteriorated. Because there are no guidelines regarding how to treat SJS/TEN patients who are refractory to glucocorticoids and IVIG, the studies mentioned above prompted us to conduct hemoperfusion for these patients.

The current directions for hemoperfusion therapy do not include patients with SJS/TEN. Therefore, the number of hemoperfusion sessions in our study was justified by the severity of SJS/TEN and the treatment response to hemoperfusion. We performed hemoperfusion until new skin lesions stopped appearing and the skin started to heal with visible re-epithelialization. The hemoperfusion sessions were conducted daily. Spacing the treatments daily ensures that the desired therapeutic effect is achieved as quickly as possible. Although a statistical analysis was impossible due to our small sample size, our preliminary data demonstrate the beneficial effects of hemoperfusion in treating patients with severe SJS/TEN. Hemoperfusion rapidly relieved systemic symptoms, prevented new eruptions and mucous membrane exudation, reduced febrile durations, and shortened the disease duration. More importantly, all ten patients survived and recovered completely. Although we did not detect changes in the "harmful substances" in the blood before and after hemoperfusion, we speculated that hemoperfusion acts by effectively removing the drugs or their metabolites[22] or by removing immune complexes and medium-sized inflammatory mediators[19-21].

Previous studies have indicated that plasmapheresis relieved severe TEN[23-30]. Because SJS and TEN are rare and occur unpredictably, only a non-blinded, uncontrolled study was conducted in our study. However, plasmapheresis requires plasma, which is expensive, and can result in transfusion-related adverse reactions. The equipment used for hemoperfusion is simple and requires only a blood pump, tools for vascular access, and a hemoperfusion device. Hemoperfusion can be operated at the bedside and is easily performed in primary hospitals. The hemoperfusion device can rapidly clear serum bilirubin, thereby reducing its toxic effects, which improves systemic effects and normalizes hepatic function. If severe SJS/TEN is accompanied by severe drug-induced hepatitis, hemoperfusion should be immediately performed. If severe SJS/TEN is accompanied by acute renal failure or multiple organ dysfunction, other blood purification techniques (i.e., hemodialysis and continuous blood purification) must be combined to achieve satisfactory outcomes. Of course, hemoperfusion only promptly removes the "harmful substance", such as the drug and inflammatory mediators. Therefore, glucocorticoids still should be used to control the inflammatory immune reaction.

Although hemoperfusion is a simple procedure, adverse reactions may occur in seriously ill patients. During the course of hemoperfusion, hypotension, nausea, vomiting, palpitations, shortness of breath, chest tightness, chills and

other adverse reactions may occur[31]. In our study, the most serious adverse reaction was femoral vein thrombosis; other adverse reactions were few and mild. Previous studies have indicated that catheter-related femoral venous thrombosis is the most common adverse reaction to hemoperfusion[32], occurring in children with indwelling femoral vein catheters, often within 48 hour after catheter placement. Even three days after catheter placement, the occurrence of thrombosis formation remained high[32]. Currently, there is no evidence suggesting that heparin can prevent pediatric catheter-related thrombosis[33]. Due to coagulation imbalances, patients with severe SJS/TEN are often hypercoagulable[34]. Hence, patients with severe SJS/TEN have a greater risk of deep vein thrombosis. Signs of catheter-related thrombosis should be monitored, particularly in the limbs (i.e., symmetry of the limbs). For patients with limb swelling or asymmetry, the femoral vein catheter should be promptly removed, and thrombolysis and anticoagulation therapy should be applied.

Conclusions

Hemoperfusion may be a useful adjunct treatment for patients with severe SJS/TEN if the initial treatment with glucocorticoids and IVIG fails. The early application of hemoperfusion demonstrated beneficial effects and improved the outcomes of patients with SJS/TEN. However, hemoperfusion is an invasive therapy, and the indications for its use must be strictly followed. Hemoperfusion should be used in patients with refractory SJS/TEN that is uncontrolled by systemic glucocorticoids and IVIG. Prospective studies are needed to fully investigate the efficacy of hemoperfusion in patients with refractory SJS/TEN.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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