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치료적 혈장교환술 시행 중 발생한 사람혈청알부민에 대한 과민반응 2예

Two Cases of Hypersensitivity Reactions Caused by Human Serum Albumin During Therapeutic Plasma Exchange

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Iso-oncotic human serum albumin (HSA) is the primary replacement fluid of choice during therapeutic plasma exchange (TPE). Hypersensitivity reactions to HSA are rare, but require proper evaluation and management. In this article, we report two cases of hypersensitivity reactions to 5% HSA during TPE and discuss strategies to address this problem. The first case was a 60-year-old female patient, who was scheduled for TPE for treatment of recurrent focal segmental glomerulosclerosis after ABO-incompatible kidney transplantation. She developed a pruritic rash on her entire body during the first two sessions of TPE using 5% HSA. The third session was conducted using 500 mL normal saline, 1,000 mL 10% pentastarch, and 750 mL 5% HSA, where she eventually developed a pruritic rash when HSA was infused. There were no adverse events during the fourth and fifth session when fresh frozen plasma was used in place of HSA. The second case was a 50-year-old male patient diagnosed with optic neuritis, who was admitted for five sessions of TPE. The patient developed a pruritic rash on his entire body during the first session of TPE using 5% HSA. The patient experienced no adverse events during the following four sessions using fresh frozen plasma. Certain elements contained in HSA, such as albumin aggregates, prekallikrein activator, and caprylate-modified albumin, might be the reason for these hypersensitivity reactions. Careful selection of alternative replacement fluids is important to avoid premature termination of TPE procedures and secure optimal treatment options for patients.

Key Words: Human serum albumin, Hypersensitivity, Plasma exchange, Prekallikrein activator, Caprylates, Albumin aggregates

INTRODUCTION

During therapeutic plasma exchange (TPE), it is necessary to provide an adequate colloid-containing solution to replace removed plasma. Although it may lead to a transient decline in the levels of many plasma components, iso-oncotic 4–5% human serum albumin (HSA) in normal saline is the primary replacement fluid of choice for TPE. Fresh frozen plasma (FFP) is reserved for use in patients with thrombotic thrombocytopenic purpura and other indications where replenishing normal plasma proteins, such as coagulation factors, is considered essential [1]. Allergic reactions due to antibody-mediated hypersensitivity are the most common adverse events associated with FFP transfusion. Plasma proteins, such as haptoglobin, immunoglobulin A (IgA), and C4, are responsible for anaphylactic reactions in patients with deficiencies; however, the offending plasma protein is not easily identifiable in most instances [2, 3]. Hypersensitivity reactions to HSA, albeit very rare, have been previously published [4-8], but there are limited data on these reactions in the Korean population [9].

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Herein, we report two cases of hypersensitivity reactions to 5% HSA during TPE and briefly discuss possible strategies to address this problem in the TPE setting.

CASES

1. Patient 1

A 60-year-old female patient was admitted to a tertiary hospital in Seoul and scheduled for TPE for treatment of biopsy-confirmed recurrent focal segmental glomerulosclerosis. The patient's vital signs on admission were a blood pressure of 131/77 mmHg, heart rate of 91 beats/min, respiratory rate of 18 breaths/min, and body temperature of 37.0℃. The patient underwent ABO-incompatible kidney transplantation at the same hospital 4 years previously and 16 TPE procedures were conducted during the pre- and post-transplant periods without the occurrence of any adverse events, including hypersensitivity reactions, from use of 5% HSA (Human Serum Albumin Injection 5%, Greencross, Yongin, Korea) and FFP as the replacement fluid in nine and seven TPE procedures, respectively. The composition of the HSA solution used is shown in Table 1. The amount of each component per unit was not disclosed.

On the second day of admission, the patient underwent the first TPE session using 5% HSA. A few minutes after commencement of the procedure, the patient developed a pruritic rash on her entire body. Several minutes following the onset of symptoms, the patient's vital signs were a blood pressure of 142/82 mmHg, heart rate of 99 beats/min, respiratory rate of 20 breaths/min, and body temperature of 37.0℃. TPE was eventually discontinued because the patient's symptoms persisted despite treatment with 8 mg chlorpheniramine and 100 mg hydrocortisone. On the fourth day of admission, the patient was premedicated with 4 mg chlorpheniramine before the second TPE. However, the patient once again developed pruritus just a few minutes after the procedure began using 5% HSA. Several minutes following the appearance of symptoms, the patient's vital signs were a blood pressure of 117/73 mmHg, heart rate of 75 beats/min, respiratory rate of 20 breaths/min, and body temperature of 36.8℃. Fortunately, the patient's symptoms became tolerable with additional doses of 8 mg chlorpheniramine and 100 mg hydrocortisone and the TPE was completed as intended. The third session of TPE was conducted on the sixth day of admission. To minimize the use of HSA, the removed plasma was replaced sequentially with 500 mL normal saline (Sodium Chloride Injection 0.9%, CJ HealthCare, Seoul, Korea), 1,000 mL 10% pentastarch (Pentaspan Injection 10%, Jeil Pharmaceutical Co., Ltd., Seoul, Korea), and 750 mL 5% HSA. Although the patient was premedicated with 4 mg chlorpheniramine, she eventually developed a pruritic rash on her entire body about 30 minutes after administration of 5% HSA was started. Several minutes after the onset of symptoms, the patient's vital signs were a blood pressure of 102/56 mmHg, heart rate of 90 beats/min, respiratory rate of 20 breaths/min, and body temperature of 37.0℃. Treatment with 8 mg chlorpheniramine and 100 mg hydrocortisone made the patient's suffering tolerable and TPE was completed without cessation.

The next two sessions of TPE were performed with FFP on the eighth and tenth days of admission. Premedication with 4 mg chlorpheniramine was provided and the TPEs were completed without any adverse events. The apheresis machines used for the TPEs were a COBE Spectra (Terumo BCT, Lakewood, CO, USA) and Plasauto EZ (Asahi Kasei Medical, Tokyo, Japan).

Table 1. Components of human serum albumin injection

Components
Human albumin
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Sodium N-acetyltryptophanate
Sodium caprylate
Water for injections

2. Patient 2

A 50-year-old male patient previously diagnosed with optic neuritis presented to a tertiary hospital in Seoul with sudden-onset blurred vision in the left eye. The patient had no prior history of transfusion and was admitted for five sessions of TPE. The patient's vital signs on admission were a blood pressure of 132/76 mmHg, heart rate of 94 beats/min, respiratory rate of 18 breaths/min, and body temperature of 37.0℃. The first TPE session was conducted with 5% HSA on the second day of admission. Several minutes after the procedure had commenced, the patient developed a pruritic rash on his entire body. A few minutes following the onset of the symptoms, the patient's vital signs were a blood pressure of 149/99 mmHg, heart rate of 104 beats/min, respiratory

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Table 2. Clinical features of the TPE procedures performed in the two patients

	Replacement fluid and infused volume	Anticoagulant	Apheresis machine	Adverse event
Patient 1				
TPE #1	5% HSA: 2,320 mL	Heparin	Plasauto EZ	Pruritus and erythematous rash
TPE #2	5% HSA: 2,430 mL	Heparin	Plasauto EZ	Pruritus and erythematous rash
TPE #3	NS: 500 mL 10% Pentastarch: 1,000 mL 5% HSA: 750 mL	ACD	COBE Spectra	Pruritus and erythematous rash against 5% HSA
TPE #4	FFP: 2,186 mL	ACD	COBE Spectra	None
TPE #5	FFP: 2,310 mL	ACD	COBE Spectra	None
Patient 2				
TPE #1	5% HSA: 2,320 mL	Heparin	Plasauto EZ	Pruritus and erythematous rash
TPE #2	FFP: 2,954 mL	ACD	COBE Spectra	None
TPE #3	FFP: 2,992 mL	ACD	COBE Spectra	None
TPE #4	FFP: 3,120 mL	ACD	COBE Spectra	None
TPE #5	FFP: 3,040 mL	Heparin	Plasauto EZ	None

Abbreviations: TPE, therapeutic plasma exchange; HSA, human serum albumin; NS, normal saline; FFP, fresh frozen plasma; ACD, acid citrate dextrose.

rate of 20 beats/min, and body temperature of 37.5°C. The patient's symptoms were refractory to treatment with 8 mg chlorpheniramine and 100 mg hydrocortisone, and therefore, the TPE was prematurely terminated. The following four sessions of TPE were performed with FFP. Before each procedure, the patient was medicated with 4 mg chlorpheniramine and hypersensitivity reactions were not reported during these procedures. The replacement fluids and infused volumes, anticoagulants, and apheresis machines used and adverse events experienced for both Patients 1 and 2 are summarized in Table 2.

DISCUSSION

Albumin contributes 70–80% of the oncotic pressure of normal plasma, which averages 4.2 g/dL [1]. Twenty-three different allotypes of albumin have been reported for human sera [8]. HSA is purified from large pools of donated human plasma using variations in the Cohn fractionation technique. Purified albumin is heated to 60°C for 10 hr, which effectively pasteurizes the product and inactivates viruses. Additional steps in the fractionation process are taken to inactivate or remove heat-stable viruses, such as the hepatitis A virus and parvovirus [10]. In addition to reduced risk of viral transmission, other adverse events, including hypersensitivity reactions, occur less frequently with HSA than FFP [1]. Generally, hypersensitivity reactions resolve spontaneously when infusion of the problematic solution has been stopped and the patient has responded well to treatment or premedication with antihistamines and/or corticosteroids. In rare cases, however, severe or potentially life-threatening reactions requiring prompt recognition and immediate management occur [11]. In the two patients discussed in this study, the hypersensitivity reactions were generally mild to moderate, involving only cutaneous manifestations, such as erythematous rash and pruritus. Although potentially life-threatening symptoms involving the respiratory and/or cardiovascular systems observed in anaphylactic reactions, such as airway compromise and severe hypotension requiring vasopressor treatment, were not present in our patients, mucocutaneous symptoms that do not respond to medication can imbue the patient with great discomfort and suffering, especially if these symptoms involve the entire body, and lead to premature termination of TPE. To sustain an adequate number of TPEs necessary for the patient, it is important to identify the cause of associated adverse reactions regardless of severity and select appropriate alternative replacement fluids.

Currently, the purity of HSA is typically 99% [8]. However, contaminants such as other plasma proteins, prekallikrein activator (PKA), and albumin aggregates can render albumin infusion intolerable [12]. In our two patients, hypersensitivity reactions to FFP, which contains much higher levels of other plasma proteins than HSA, were not observed during TPE. Therefore, it is very unlikely that plasma proteins other than albumin were the causative agent underlying the hypersensitivity reactions. HSA is preferred over less pure albumin preparations such as plasma protein fraction, which contains higher levels of PKA and is therefore more likely

to induce vasodilation and hypotension through bradykinin generation [6, 13]. Nevertheless, some HSA contains appreciable levels of PKA that are capable of causing hypersensitivity reactions [14]. Stabilizers, such as caprylate and N-acetyltryptophanate (NAT), are added to pharmaceutical-grade HSA during manufacturing to prevent thermal degradation and aggregation [15]. However, the formation of protein aggregates may occur despite the use of stabilizers and hypersensitivity reactions against HSA aggregates have been previously described [7]. The mechanism by which HSA aggregates induce hypersensitivity reactions has yet to be defined. The hypersensitivity reactions against HSA in our two patients might be explained by PKA contamination or HSA aggregates formed during commercial production.

Stabilizers can play another role in hypersensitivity reactions with HSA. Experimental evidence indicates caprylate-modified albumin can induce antibody formation [16]. Ring et al. [7] described antibodies against caprylate-modified albumin as a potential cause of hypersensitivity in two patients who reacted to caprylate-modified albumin in the absence of a response to monomeric native albumin during the skin test. Hypersensitivity reactions to albumin modified by NAT have not been previously reported. The HSA solution used in our patients contained both caprylate and NAT. The stabilizers used in HSA are not present in FFP. Considering that our patients displayed hypersensitivity only to HSA and not FFP and hypersensitivity reactions to albumin molecules modified by NAT have not yet been reported, caprylate-modified albumin can also be considered a possible cause. Previous exposure to caprylate-modified albumin, although it did not cause immediate hypersensitivity reactions, might have successfully sensitized Patient 1. During TPE using HSA as the replacement fluid, re-exposure to caprylate-modified albumin could have triggered the patient's hypersensitivity reactions.

The TPEs performed on our two patients were based on centrifugation (cTPE) and membrane filtration (mTPE), which are both well-established procedures. Although cTPE has a higher plasma removal efficiency during a shorter treatment duration, the declines in markers of procedural efficacy are comparable [17]. Hence, our institution has no preference between cTPE and mTPE beyond taking into consideration whether patients have problems using heparin as the anticoagulant. Activation of the complement cascade has been observed in mTPE, but not cTPE [18]. However, hypersensitivity reactions also occurred during cTPE using the COBE Spectra in Patient 1. It is more likely that the possible culprit of hypersensitivity reactions in our cases was a certain element contained in HSA rather than membrane filtration.

When hypersensitivity reactions to HSA do not respond to symptomatic treatment, infusion of HSA must be stopped [3]. During laboratory examinations, contaminating plasma proteins other than albumin need to be considered first as causative agents. Plasma levels of IgA, C4, and haptoglobin and their corresponding IgG and IgE antibodies should be evaluated [9]. Furthermore, skin prick, intradermal, and specific IgE tests can be performed against aggregated or chemically modified HSA [5]. Unfortunately, the results of these tests were unavailable for our two patients. In these patients, alternative replacement fluids, including crystalloid, synthetic colloid, and FFP, were infused without incurring any adverse reactions during TPE. We presumed certain factors inherent in HSA, such as albumin aggregates, PKA, or caprylate-modified albumin, may have contributed to the hypersensitivity reactions in our two patients. All HSA solutions used in the two patients were produced by the same manufacturer, but their lot numbers were not recorded. Therefore, the effect of lot-to-lot variability on these hypersensitivity reactions could not be evaluated.

When HSA is suspected as the culprit of hypersensitivity reactions during TPE, there is no standardized protocol for selection of alternative replacement fluids. Regarding HSA production, manufacturer-to-manufacturer and lot-to-lot variability exist in terms of albumin aggregate content, plasma protein contamination, and types of stabilizers and albumin variants. Therefore, replacement with HSA from different manufacturers or different lots from the same manufacturer could be a first option. If the replacement HSA continues to produce hypersensitivity reactions, crystalloid solutions can be used as alternative replacement fluids because they lack allergic potential. However, crystalloids have less of a volume-sparing effect and more potential to induce clinically significant interstitial edema compared to HSA [19]. As for synthetic colloids, hydroxyethyl starches (e.g., pentastarch) are frequently used, while dextrans and gelatins are less commonly used [19]. Although synthetic colloids are relatively inexpensive, they are associated with a higher increased risk of adverse reactions than HSA, possibly due to their non-human origin [20]. FFP is also an alternative choice to HSA, particularly when albumin aggregates or caprylate-modified albumin are considered causative agents of the hypersensitivity reaction. When dilutional coagulopathy due to the infusion of

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crystalloids or synthetic colloids is expected, FFP is a reasonable choice. However, we should always keep in mind that the use of FFP as a replacement fluid is associated with increased risk of viral transmission, hypersensitivity reactions, and citrate toxicity compared with crystalloids and synthetic colloids [1]. Replacement with crystalloids alone carries the risk of peripheral edema [21] and therefore should be restricted to small-volume plasma exchange. Combining crystalloids with synthetic colloids and/or FFP would be a better alternative in a typical clinical setting. Synthetic colloids or FFP alone can also be used as an alternative to circumvent the hypersensitivity reactions associated with HSA, particularly when the risk of peripheral edema is high and the adverse effects of synthetic colloids or FFP are relatively tolerable. The replacement fluid selection is made on an individual case-by-case basis, where the patient's entire clinical picture is taken into account. The proposed algorithm described above for replacement fluid selection is shown in Fig. 1.

If the use of HSA is unavoidable, treatment with a stepwise desensitization protocol can also be considered as a reasonable option [9]. Although desensitization has medium- to long-term benefits, this strategy may not be feasible in short-term TPE situations.

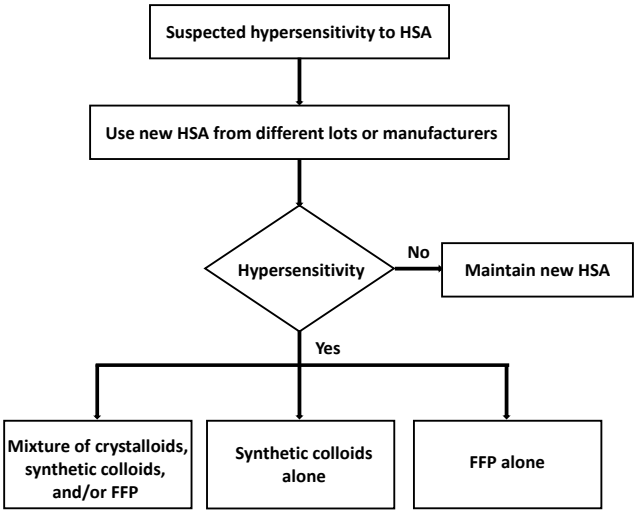

Fig. 1. Proposed algorithm for replacement fluid selection when hypersensitivity to HSA is suspected during TPE. Replacement with HSA from different lots or manufacturers should be the first choice. If infusion of the new HSA still leads to hypersensitivity reactions, the following three options are recommended: 1) a mixture of crystalloids, synthetic colloids, and/or FFP, 2) synthetic colloids alone, or 3) FFP alone.
Abbreviations: HSA, human serum albumin; FFP, fresh frozen plasma; TPE, therapeutic plasma exchange.

Depletion of stabilizers from HSA through adsorbents or dialysis before infusion also helps prevent hypersensitivity reactions to stabilizer-modified HSA [22]. However, these methods are technically demanding and their use in routine clinical practices is currently questionable.

To the best of our knowledge, this is the first report of hypersensitivity reactions to HSA during TPE in Korea. Our two patients developed hypersensitivity reactions to 5% HSA, and certain elements contained in HSA, such as albumin aggregates, PKA, and caprylate-modified albumin, may be the culprit(s) underlying these hypersensitivity reactions. The use of crystalloids, synthetic colloids, and FFP did not lead to any hypersensitivity reactions in our patients, who were successfully treated with TPE as scheduled. Careful selection of alternative replacement fluids is important to avoid premature termination of TPE and secure optimal treatment for patients.

요 약

등장성 사람혈청알부민은 치료적 혈장교환술에서 1차 치환용액으로 흔히 사용된다. 사람혈청알부민에 대한 과민반응은 매우 드물게 발생하지만, 적절한 평가와 관리가 필요하다. 저자들은 5% 사람혈청알부민을 사용한 혈장교환술 시행 중 발생한 과민반응 2예를 보고하고 이러한 상황에 대처하는 방안에 대해 기술하였다. 첫 번째 증례는 ABO 부적합 신장이식을 받았던 60세 여자 환자가 반복적으로 발생하는 국소분절사구체경화증을 치료하기 위해 혈장교환술을 받게 되었다. 5% 사람혈청알부민을 사용한 첫 두 회의 혈장교환술에서 전신에 가려움증과 발진이 발생하였다. 세 번째 혈장교환술에서는 생리식염수 500 mL, 10% pentastarch 1,000 mL, 그리고 5% 사람혈청알부민 750 mL를 사용하였으나, 사람혈청알부민 주입 후에 결국 전신적인 가려움증과 발진이 발생하였다. 신선동결혈장을 사용한 네 번째와 다섯 번째 혈장교환술 중에는 부작용이 발생하지 않았다. 두 번째 증례는 시신경염 진단을 받은 50세 남자 환자가 치료를 위해 5회의 혈장교환술을 받게 되었다. 5% 사람혈청알부민을 사용한 첫 회의 혈장교환술에서 전신에 가려움증과 발진이 발생하였다. 신선동결혈장을 사용한 나머지 네 번의 시술에서는 부작용이 관찰되지 않았다. 이처럼 사람혈청알부민 사용시에만 발생하는 과민반응의 원인으로 알부민 응집체, 프리칼리크레인 활성인자 및 카프릴레이트-변형 알부민이 있을 수 있다. 혈장교환술을 조기에 종료하는 것을 피하고 환자에게 최적의 치료를 제공하기 위해서는 대체 치환용액을 잘 선정하여 사용하는 것이 중요하다.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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