Original Article

Safety and Efficacy of the Thai Red Cross Society Albumin Replacement for Therapeutic Plasma Exchange

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Background: Albumin replacement has been widely used in various conditions. However, there had been problems of rising cost and supply shortage of imported albumin in Thailand. To solve the problem, the National Blood Centre had established a plasma fractionation plant to manufacture plasma products including albumin.

Objective: To evaluate the safety and efficacy of the Thai Red Cross Society [TRCS] albumin.

Materials and Methods: To minimize confounder effects of underlying conditions, only patients that underwent therapeutic plasma exchange [TPE] using the TRCS albumin replacement from two hospitals were included. Serum albumin levels were measured before and after TPE. The adverse effects were recorded.

Results: One hundred fifty-six TPEs in 35 patients were included. The median total plasma volume was 3,000 (range 1,750 to 4,200) mL. Although the corrected calcium level was low (<8 mg/dL) in 3.2% (5/156) before the procedure, no clinical manifestation of hypocalcemia was detected. Adverse effects were observed during the TPE in two patients. The first patient had two events of hypotension. He previously took angiotensin converting enzyme inhibitor. The second patient complained of nausea after finishing TPE. The incidence of adverse effects was 1.9% (3/156). As a historical control, the incidence of TPE adverse effects was 1.6% (2/125) when commercial albumin was used in 2014. The difference was not statistically different (p = 1.000). Median serum albumin levels pre-TPE and post-TPE were 3.6 (1.9 to 4.4) and 3.9 (2.4 to 5.0) g/dL, respectively. The increase in serum albumin after TPE was statistically significant (p<0.001).

Conclusion: The authors demonstrated that the TRCS albumin was safe and effective in maintaining albumin levels in patients undergoing TPEs.

Keywords: Therapeutic plasma exchange, Albumin

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Albumin is the majority of circulating protein and accounts for about 70% of the plasma colloid osmotic pressure[1]. It is widely used in clinical practice for many indications such as cirrhosis, hypovolemia, shock, spontaneous bacterial peritonitis with ascites, post-paracentesis syndrome, or treatment of hepatorenal syndrome as an adjunct to vasoconstrictors[2,3]. Albumin solution is purified from a large pool of human plasma. Compared with the whole plasma replacement, albumin has lower incidence of transfusion reactions, no requirement of thawing and no risk of disease transmission. However, there had been rising cost and supply shortage of imported albumin in Thailand. To solve the problem, the National Blood Centre, Thai Red Cross Society [TRCS] had established a plasma fractional plant to manufacture plasma derivatives including albumin with the collaboration and technology transfer from the South Korea-based Green Cross Corporation.

Therapeutic plasma exchange [TPE] with albumin replacement has been used to treat a variety of diseases such as myasthenia gravis [MG], systemic lupus erythematosus [SLE], and hyperviscosity in monoclonal gammopathies[4]. The primary goal of the procedure is to remove pathologic substances (e.g.,

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autoantibodies, immunoglobulins, immune complexes, or cytokines) by removing the plasma component. When a large volume of plasma is removed during TPE, 4% to 5% human albumin in physiologic saline is mostly used as a replacement fluid to prevent hypotension and peripheral edema[5,6].

The objective of the present study was to evaluate the safety and efficacy of the TRCS albumin. As there are potentially many adverse events from underlying conditions in patients requiring albumin replacement, the authors recruited patients who underwent TPE and compared to the historical controls of TPE using imported albumin.

Materials and Methods

Study population

The present study was approved by the Institutional Review Boards [IRBs] of the participating Institutes. All patients who fulfilled the indication for TPE with albumin replacement at King Chulalongkorn Memorial Hospital and Prasat Neurological Institute between June 2016 and February 2017 were included. If plasma was used as a replacement fluid for TPE, the patient was excluded from the study. The demographic data of the patients were collected.

Prior and post procedure

Blood was drawn from participants for complete blood count [CBC], calcium, and albumin prior to the procedure. A physician determined whether the participant was suitable for TPE. The acceptable results were hematocrit greater than 25%. The central catheterization was done if they could not get the best assess from the peripheral line. All the patients were hospitalized and received oral calcium before TPE to prevent hypocalcemia. Vital signs were checked before the beginning of TPE. At the end of the procedure, blood for serum albumin was drawn.

Therapeutic plasma exchange procedure

TPE was performed at the Transfusion Medicine Unit at King Chulalongkorn Memorial Hospital and Prasat Neurological Institute by experienced apheresis technicians under the supervision of physicians. The apheresis machine was set up according to the manufacturer's instructions (Spectra Optia or Fresenius). The TRCS albumin was available as a 20% solution. Before using, it was diluted to a 4% albumin concentration with normal saline. The central line was connected to a continuous flow apheresis device. The cell separator kit was anticoagulated with acid citrate dextrose-A [ACD-A], with a whole blood-to-anticoagulant ratio of 13:1. Blood was withdrawn from the venous line and channeled to the cell separator where the plasma fraction is separated by centrifugation. The apheresis technician monitored the participant during the procedure and was prepared to handle adverse events.

Table 1. Classification of adverse effects of therapeutic plasma exchange

Severity	Definition
Mild	No medical intervention; procedure not delayed
Moderately severe	Not life threatening: medical intervention and/or delay of procedure required; no procedures terminated
Severe	Life threatening and/or procedure terminated
Fatal	Death during or associated with plasma exchange

Methodology to defining adverse effects

All the study patients were admitted into the hospitals. The adverse effects were recorded during TPE and 24 hours after TPE. The severity of adverse effects was graded in severity according to Table 1[7].

Sample size calculation

According to the data in 2014, the incidence of adverse effects at King Chulalongkorn Memorial Hospital was 1.6%. With 95% confidential interval and allowable error of 0.05, the sample size was about 80 TRCS albumin administrations.

Statistical analysis

All statistical analysis was done using SPSS version 16. Fisher's exact test was used for the comparison of the categorical outcomes (adverse effects) between the data in 2014 and the data in our study. Wilcoxon signed rank test was used for comparison of the continuous outcome (serum albumin level) prior and post TPE. Wilcoxon signed rank test was assumed one-sided significance and Fisher's exact test was assumed two-sided significance. Significance was determined at p-value smaller than 0.05 for all calculations.

Results

Patient characteristics

Thirty-five patients had TPE performed with TRCS albumin between June 2016 and February 2017. One hundred fifty-six TPEs in 35 patients were included. The median age of the patients was 36 years (range 13 to 87) with the median weight of 59 kg (range

Table 2. Indications for therapeutic plasma exchange [TPE]

Indication	Number of patients n (%)	Number of TPE n (%)
Neuromyelotis optica spectrum disorders	10 (28.6)	47 (30.1)
Systemic lupus erythematosus	6 (17.1)	33 (21.1)
Amyotrophic lateral sclerosis	4 (11.4)	21 (13.5)
Myasthenia gravis	3 (8.6)	15 (9.6)
Rapidly progressive glomerulonephritis	3 (8.6)	9 (5.8)
Nephropathy with acute kidney injury	1 (2.9)	5 (3.2)
Pemphigus vulgaris	1 (2.9)	5 (3.2)
Renal transplantation	1 (2.9)	2 (1.3)
Systemic vasculitis	1 (2.9)	3 (1.9)
Thyroid cancer	1 (2.9)	3 (1.9)
Severe aplastic anemia post ABO mismatch stem cell transplant	1 (2.9)	1 (0.7)
Autoimmune encephalitis	1 (2.9)	6 (3.8)
Pulmonary hemorrhage	1 (2.9)	1 (0.7)
Transverse myelitis	1 (2.9)	5 (3.2)

13 to 89) and the median height of 160 cm (range 132 to 175). They were composed mainly of females (24 patients, 71%). Neurologic disorders were the most common indication for TPE, followed by autoimmune diseases as shown in Table 2.

Therapeutic plasma exchange

All of the procedure were done through a central line. The median total plasma volume was 3,000 (range 1,750 to 4,200) mL. The median volume treated was 1.15 total plasma volume, range 0.87 to 1.67.

Adverse effect of therapeutic plasma exchange

The overall incidence of adverse effect was 1.9% (3/156). Two of the adverse effects were classified as moderately severe and one was classified as mild. No severe and fatal reaction was detected in the present study. Two events of symptomatic hypotension during the procedure were detected in the same patient. Those were considered as moderately severe reaction. This patient previously took angiotensin converting enzyme inhibitor [ACEI] before the procedure. One mild event of nausea was identified in another patient after finishing TPE. All adverse effects were reversible reactions. There was no clinical manifestation of hypocalcemia detectable, although the corrected calcium level was low (less than 8 mg/dL) in 3.2% (5/156) before the procedure.

In 2014, the imported albumin was used for TPE replacement. During the time, the incidence of TPE adverse effects was 1.6% (2/125), one event of allergic reaction and one event of hypocalcemia. The difference of adverse effects between TRCS albumin and imported albumin was not statistically different (p = 1.000).

Serum albumin level

The difference of TRCS albumin and imported albumin for TPE was the percent of albumin in the product. The final concentration of diluted TRCS albumin was 4%. The commercial imported albumin, which was ready to use, had a concentration of 5%. The serum albumin level was tested pre and post procedure to compare the loss of albumin after TPE when diluted TRCS albumin at the concentration at 4%. Interestingly, serum albumin at post procedure (median 3.9 g/dL, range 2.4 to 5.0) was significantly higher than those at pre-procedure (median 3.6 g/dL, range 1.9 to 4.4), p<0.001. Eighty-two percent of pre-TPE serum albumin levels were lower than 4.0 g/dL.

Discussion

In the present study, the authors present their experience of using TRCS albumin as the replacement fluid in TPE. The primary objective of the study was to assess the safety of TRCS albumin and historically compared with imported commercial albumin. There was no statistically significant difference between these groups in term of adverse effects. The replacement of plasma removed in TPE with 4% albumin was not different compared with 5% albumin in term of hypotension and edema. The dilution method is not complicated, and the price is cheaper than the commercial product. None of the study patients experienced infectious complication from the TRCS albumin. There were two reports of mild hypotension during TPE in the same patient. Hypotensive reaction in patients received ACEI had been reported[8]. The hypotensive mechanism was due to the enhanced bradykinin release caused by a trace amount of prekallikrein activator in albumin. Moreover, one patient reported nausea after finished TPE, which was probably unrelated to TRCS albumin. It could be the result of the patient's underlying disease, vasovagal effects, or citrate effects. Serum calcium was not performed at that time.

The incidence of all reported serious non-fatal and fatal adverse effects was 5.28 per 10^6 doses in the recent studies by 10 major suppliers of therapeutic human albumin between 1998 and 2000[9]. No patient death was classified as probably related to albumin administration. The incidence of fatal serious adverse effects possibly related to albumin was 0.185 per 10^6

doses from anaphylactic shock, toxicoderma with respiratory insufficiency, cardiac arrest, and apnea. Compared with the previous study of the safety of human albumin[9], the authors did not observe serious adverse effects in the present study. Because the incidence of adverse effect appeared to be rare, post marketing surveillance should be conducted to raise awareness of albumin related adverse effects.

Hypocalcemia was not detected in the present study. At the study center, there was hypocalcemic reaction in patients performing TPE with plasma replacement more often than those with albumin replacement. Albumin is produced from large pool of human plasma. Therefore, there is some citrate from the starting human plasma that could lower serum calcium during TPE. Previous reports showed that both total and ionized calcium levels dropped during TPE with albumin replacement[6,10]. This could be the result from citrate use in apheresis circuit and citrate in albumin product. To increase serum calcium level in the patient after the decline of serum calcium during TPE by physiologic mechanism, N-terminal parathyroid hormone and urine cyclic adenosine monophosphate levels were increased[10]. The use of calcium supplement to prevent symptoms and signs of hypocalcemia is controversial. The authors usually give oral calcium to patients when TPE was started. In some cases with low or borderline serum calcium, another dose of oral calcium was given again during TPE. Compared with the previous study, the incidence of hypocalcemia in the patient undergoing TPE with calcium supplementation was 8.6%, which was higher than the present study[11]. A limitation of the present study was the difference in calcium supplement. The supplement was a part of the present study protocol. In 2014, calcium was not given to all patients. This could lead to no hypocalcemia in the present study, but one hypocalcemia in the historical cohort.

Serum albumin levels post-TPE were higher than those of pre TPE. Most of the patients had serum albumin levels lower than 4.0 g/dL before the procedure, resulting in the increase in the levels after TPE with 4% albumin replacement. Most patients were admitted to the hospital for some time before TPE because TPE was not considered as the first-line therapy for the patients. Therefore, serum albumin levels were low in most patients at baseline.

Albumin is also widely used in patients for many clinical indications[12]. The volume of TRCS albumin use in TPE ranged from 350 to 850 mL per procedure, which was much greater than those of other indications. However, the authors could not detect any allergic or fever reactions from TRCS albumin. From this observation, the authors may draw the assumption that the TRCS albumin is relatively safe in other indications too. Further studies of the adverse effects and efficacy of the TRCS albumin in other indications will prove the assumption.

Conclusion

The authors demonstrated that the TRCS albumin was safe. No severe adverse effect was detected in the present study. The TRCS albumin was also effective in maintaining normal albumin levels in patients undergoing TPEs.

What is already known on this topic?

Albumin is widely used in clinical practice for many indications. It has been used as a replacement fluid in TPE due to low incidence of transfusion reaction and no risk of infection.

What this study adds?

The TRCS albumin, produced by the TRCS is relatively safe to use in patients undergoing TPEs. Using the TRCS albumin could solve the problem of rising cost and supply shortage of imported albumin in Thailand.

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The TRCS albumin used in the present study was donated by the TRCS.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Caraceni P, Domenicali M, Tovoli A, Napoli L, Ricci CS, Tufoni M, et al. Clinical indications for the albumin use: still a controversial issue. Eur J Intern Med 2013;24:721-8.
2. Rozga J, Piatek T, Malkowski P. Human albumin: old, new, and emerging applications. Ann Transplant 2013;18:205-17.
3. Aramwit P, Kasettratat N. Evaluation of serum albumin utilization in inpatient at a private hospital in Bangkok. Yakugaku Zasshi 2004;124: 631-4.
4. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, 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 seventh special issue. J Clin Apher 2016;31:149-62.
5. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematology Am Soc Hematol Educ Program 2012;2012:7-12.
6. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. Best Pract Res Clin Haematol 2006; 19:157-67.
7. Couriel D, Weinstein R. Complications of therapeutic plasma exchange: a recent assessment. J Clin Apher 1994;9:1-5.
8. Owen HG, Brecher ME. Atypical reactions associated with use of angiotensin-converting enzyme inhibitors and apheresis. Transfusion 1994;34:891-4.
9. Vincent JL, Wilkes MM, Navickis RJ. Safety of human albumin--serious adverse events reported worldwide in 1998-2000. Br J Anaesth 2003; 91:625-30.
10. Silberstein LE, Naryshkin S, Haddad JJ, Strauss JF 3rd. Calcium homeostasis during therapeutic plasma exchange. Transfusion 1986;26:151-5.
11. Weinstein R. Prevention of citrate reactions during therapeutic plasma exchange by constant infusion of calcium gluconate with the return fluid. J Clin Apher 1996;11:204-10.
12. Soeters PB. Rationale for albumin infusions. Curr Opin Clin Nutr Metab Care 2009;12:258-64.