Original Article

Effect of Double Filtration Plasmapheresis on Various Plasma Components and Patient Safety: A Prospective Observational Cohort Study

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Abstract

Double filtration plasmapheresis (DFPP) was historically used for blood group incompatible renal transplantation. Very few studies are available worldwide regarding its efficiency in removing specific plasma components, and safety. We conducted a prospective observational cohort study over 1 year on patients undergoing DFPP for various renal indications. There were 15 patients with 39 sessions. The pre- and post-procedure plasma samples of serum IgG, IgA, IgM, fibrinogen, calcium, phosphate, potassium, and magnesium were analyzed. The effluent albumin concentration was also measured, and complications during the hospital stay were recorded. Cumulative removal of serum IgG, IgA, IgM, fibrinogen, and albumin at the end of four sessions were 72%, 89%, 96%, 88.5%, and 21.3%, respectively and effluent albumin concentration was 1.75 – 2.0 times (range: 6.3 g/dl – 7.2 g/dl; mean ± standard deviation (SD) – 7 g/dl ± 0.3 g/dl) the preprocedural serum albumin (mean ± SD – 3.5 g/dl ± 0.5 g/dl). Removal of other plasma components were not statistically significant. Hypotensive episodes were observed only 16.6%, with the usage of effluent concentration albumin as replacement fluid despite an average 2.4 (mean ± SD – 2.4 ± 0.4 l) liters of plasma volume processing each session. DFPP removes IgG, IgA, IgM, fibrinogen, and albumin. The cumulative removal IgG (72%) is suboptimal, whereas IgA (89%) and IgM (96%) are comparable to historical controls. We observed lesser episodes (12.5%) of hypotension with effluent albumin concentration as replacement fluid, and all bleeding complications were observed when serum fibrinogen level was <50 mg/dl.

Keywords: *Double filtration plasmapheresis, fibrinogen, IgA, IgG, IgM*

Introduction

Plasmapheresis, is a vital extracorporeal treatment that, aims in removing preformed antibodies and circulating factors that could eventually destroy the target organ in a short duration. It is a procedure which cannot treat the disease by itself as it can only act as a temporary measure till the drugs act and reduce the production of the target molecule.[1] Over the past few decades, various selective plasmapheresis techniques (double filtration plasmapheresis [DFPP], cascade plasmapheresis, cryofiltration, immunoadsorption, and protein A adsorption columns) are being explored to minimize patient-related complications and to maximize the removal efficiency of target molecules.[2] Immunoadsorption is a very costly alternative which can remove antibodies, provided the antigen/antibody is known and the antigen is extractable and impregnable in the adsorption column. At present, it is being used in the setting of blood group incompatible transplantation.[3] Protein A adsorption column offer selective removal of IgG alone but is expensive and has proven side effects of systemic vasculitis secondary to staphylococcal proteins.[4] Unfortunately for an emerging economy like ours, most of the available columns/filters are not reusable, which adds to the economic burden for the patient's family.

DFPP, is a method of selective plasmapheresis, pioneered by Agishi *et al.* in Japan (in the 1980's),[5] for desensitization in blood group incompatible renal transplantation. Over time, it has been used for diverse indications. In this procedure, the first filter which is called "plasma separator" separates plasma from cellular components similar to membrane filtration. Filtered plasma is allowed to pass through a second filter, which is called

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"plasma fractionator," that allows smaller molecules to pass through back into circulation and discards other molecules which are large than the pore size of the fractionator.[5]

There is a gap in knowledge on the efficiency of removal of various plasma components in DFPP worldwide and there is no literature available in the Indian context. In this study, we analyzed the efficiency of removal of various plasma components for patients with different renal indications (anti-glomerular basement disease, C3 glomerulopathy, antineutrophil cytoplasmic antibody [ANCA] vasculitis, desensitization for blood group incompatible renal transplantation, acute antibody-mediated rejection, and human leukocyte antigen [HLA] alloantibody desensitization).

Our hypothesis was that the use of DFPP can be extended to various renal indications effectively with better patient safety, lesser use of blood components, thus being a viable alternative for our patients.

Materials and Methods

Study design and setting

This is a prospective observational cohort study. Consecutive patients who underwent DFPP from December 2015 to November 2016 were included in the study. The procedure was carried out in our hospital dialysis unit.

Filter specifics

First filter (plasma separator): Plasma Flux P2 (0.6 $m^{2)}$ from Fresenius, second filter (Plasma Fractionator): Evaflux 2A (2 m^2) from Kawasumi, preseparator pump speed: 150 ml/min, prefractionator pump speed: 50 ml/min, effluent pump speed: 15–20 ml/min; effluent removal: <50 Kg – 600 ml/session; More than 50 kg – 900 ml/session.

Inclusion criteria

1. All consecutive patients (age ≥16 years) who underwent DFPP from December 2015 to November 2016.

Exclusion criteria

1. Patients who underwent DFPP for extra-renal indications
2. Patients who had conventional plasmapheresis followed by DFPP
3. Patients who had conventional plasmapheresis in between sessions of DFPP.

Data acquisition and analysis

Patients' demographics and clinical details were recorded. Pre- and post-DFPP serum levels of IgG, IgA, IgM, fibrinogen, calcium, phosphate, potassium, magnesium, and albumin were noted. Postsamples were taken immediately post-DFPP before intravenous immunoglobulin (IVIG) or dialysis if patients require any. The concentration of albumin from the discarded effluent and various complications such as hypotension, bleeding diathesis, infection, access failure, anemia, and thrombocytopenia during the procedure and hospital stay were monitored. The analysis was performed using (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.) and the value of $P \leq 0.05$ was considered statistically significant.

Primary objective

1. The proportion of removal of various plasma components in DFPP– serum IgG, IgA, IgM, calcium, phosphate, potassium, magnesium, albumin, and fibrinogen.

Secondary objective

1. Assessment of albumin concentration in the effluent
2. Complications during plasmapheresis and post plasmapharesis hospital stay were analyzed.

Results

Study population

Fifteen patients were included in the study and the total numbers of DFPP sessions were 39. Median age group of patients in the study population was 36 years (range 16–64 years) and male:female ratio was 3:2. Relevant demographics and clinical characteristics are shown in Table 1.

Number of sessions per patient varied from a minimum of one to a maximum of five with a mean of 2.6 sessions per patient. Mean plasma volume processed per patient was 2.4 l (mean ± standard deviation (SD) – 2.4 ± 0.4 l).

Time interval

After the first session of DFPP, second session treatment was given after a single day break and third session treatment was given after 2 days break. Successive sessions after third are given based on need and complication, without prefixed time interval.

Indications

Indications for DFPP in our study was distributed as follows: 33% (5/15) – desensitization for blood group incompatible kidney transplant; 27% (4/15) – acute antibody mediated rejection, 13% (2/15) each-for ANCA-associated

Table 1: Baseline characteristics

Total number of patients	15
Total number of sessions	39
Minimum number of sessions/patient	1
Maximum number of sessions/patient	5
Average plasma volume processed (L), mean±SD	2.4±0.4
Male:female	3:2
Age in years (range, median)	16-64, 36

SD: Standard deviation

vasculitis and HLA alloantibody desensitization, 7% (1/15) each for anti-glomerular basement membrane disease and C3 glomerulopathy [Figure 1].

IgG

The proportion of serum IgG removed was statistically significant (P = 0.001). Removal is assessed on a cumulative basis and per session basis. Proportional cumulative removal for four successive sessions were (mean proportion ± SD) 55 ± 16%, 70 ± 15%, 71 ± 12%, 72 ± 10% [Figure 2], respectively. Proportional serum IgG removal per successive sessions were (mean proportion ± SD) 55 ± 16%, 45 ± 19%, 44.8 ± 18%, 40.5 ± 2% respectively. Maximum serum IgG was 1840 mg/dl and the minimum was 202 mg/dl. When the pre-DFPP serum IgG level was between 200 and 300 mg/dl the removal of immunoglobulin is very minimal (approximately 25%). There is a reduction in efficiency of removal per session as shown in Table 2. Proportional IgG removal plateaued after two sessions and cumulative removal at the end of four sessions was 72 ± 10%.

IgA

Cumulative removal of IgA from session 1–4 was (mean proportion ± SD) 74% ± 11%, 84% ± 10%, 87.4% ± 8%, and 89.1% ± 4% [Figure 2], respectively, with P = 0.001. Removal per session for four successive sessions are 74% ± 11%, 62 ± 22%, 58.2% ± 6%, and 55.3% ± 12.1%, respectively. Gain in terms of cumulative efficiency of removal is much better than IgG (89% vs. 72%). The efficiency of removal decreased with each session [Table 3].

IgM

Being a larger molecule than the other two immunoglobulin, it had a higher cumulative removal through sessions one to four (mean proportion ± SD) 85% ± 13.1%, 94% ± 3.2%, 95.1% ± 1.8%, and 96. 2% ± 2.1%, respectively [Figure 2], with P = 0.001. Removal per session from session one to four were (mean proportion ± SD) 85% ± 13.1%, 57% ± 15%, 56% ± 11%, and 45% ± 18%, respectively. More than 95% of IgM is removed cumulatively at the end of four sessions [Table 4].

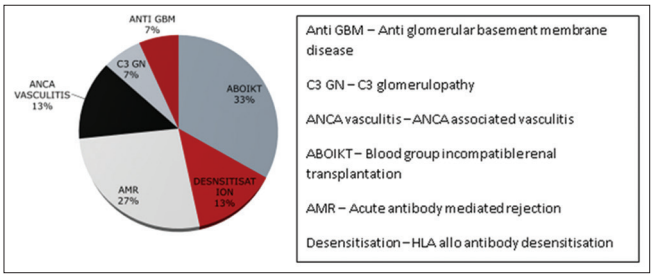

Figure 1: Indications. Anti-GBM: Anti-glomerular basement membrane disease. C3 GN: C3 glomerulopathy. ANCA vasculitis: ANCA associated vasculitis. ABOIKT: Blood group incompatible renal transplantation. AMR: Acute antibody mediated rejection. Desensitisation: HLA Allo antibody desensitisation

Fibrinogen

Removal of fibrinogen was similar to that of IgA. Cumulative removal from sessions one to four was as follows (mean proportion ± SD) 76% ± 14.8%, 83% ± 8.2%, 87 ± 10.1%, and 88.4% ± 4.2%, respectively [Figure 2], with P = 0.001. One of the Achilles heel of the procedure

Table 2: IgG removal

IgG	Proportional cumulative percentage removal (mean±SD)	Proportional per session percentage removal (mean±SD)
Session 1	55±16 (629.8±183.2 mg/dl)	55±16
Session 2	70±15 (801.5±171.7 mg/dl)	45±19
Session 3	71±12 (812.9±137.4 mg/dl)	44.8±18
Session 4	72±10 (824±114.5 mg/dl)	40.5±2

SD: Standard deviation

Table 3: IgA removal

IgA	Proportional cumulative percentage removal (mean±SD)	Proportional per session percentage removal (mean±SD)
Session 1	74±11 (173.2±25.7 mg/dl)	74±11
Session 2	84±10 (196.6±23.4 mg/dl	62±22
Session 3	87.4±8 (204.5±18.7 mg/dl)	58.2±6
Session 4	89.1±4 (208.5±9.36 mg/dl)	55.3±12.1

SD: Standard deviation

Table 4: IgM removal

IgM	Proportional cumulative percentage removal (mean±SD)	Proportional per session percentage removal (mean±SD)
Session 1	85±13.1 (53.6±8.2 mg/dl)	85±13.1
Session 2	94±3.2 (59.2±2.0 mg/dl)	57±15
Session 3	95.1±1.8 (59.9±1.1 mg/dl)	56±11
Session 4	96.2±2.1 (60.6±1.3 mg/dl)	45±18

SD: Standard deviation

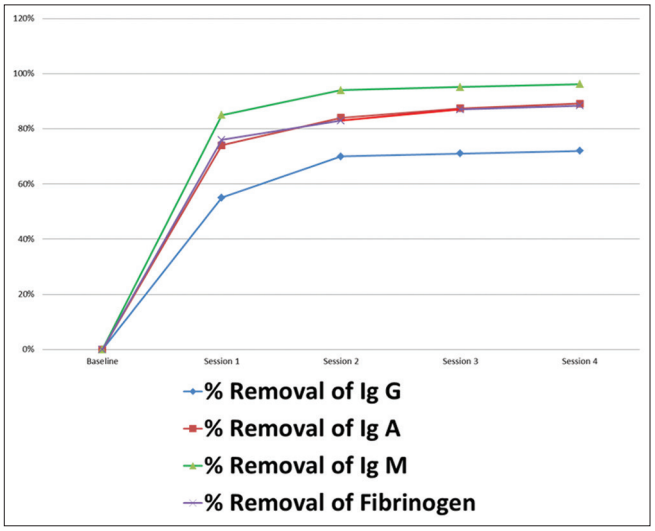

Figure 2: Removal of immunoglobulins

was this significant amount of removal of fibrinogen. All spontaneous bleeding episodes were noticed when fibrinogen levels were <50 mg/dl [Table 5].

Albumin

Mean albumin removal per session was significant with $P = 0.004$ and mean proportion of removal was 21.3%. However, the average concentration of effluent fluid albumin was 1.75 – 2.0 times (range: 6.3 g/dl – 7.2 g/dl; mean ± SD – 7 g/dl ± 0.3 g/dl) the serum albumin (mean ± SD – 3.5 g/dl ± 0.5 g/dl). The effluent albumin concentration was used to determine the concentration of replacement albumin solution. For 15/39 sessions standard albumin (5%) replacement fluid was used and for 24/39 sessions, replacement albumin concentration was same as the effluent albumin concentration which was 2% higher than the standard albumin concentration. Proportional removal percentage was 36.35% for the former and 11.9% for the latter [Table 6] ($P = 0.12$).

Other plasma components

Proportional per session removal of serum calcium ($P = 0.31$), potassium ($P = 0.55$), magnesium ($P = 0.83$), and phosphate ($P = 0.08$) was not statistically significant. None of the patient's required potassium or magnesium correction throughout the hospital stay. Calcium supplements were given only once post procedure unlike repeated replacements in conventional plasmapheresis. Changes in prothrombin time (PT) with international normalized ratio (INR), activated partial thromboplastin time (APTT) ($P = 0.43$ and 0.72, respectively), were not statistically significant [Table 7]. All postsamples were taken immediately after DFPP and before initiation of dialysis (if dialysis required) and hence, dialysis is unlikely to change the above-mentioned values in per session values but cumulative removal may change and for the same reason, plasma components removal is calculated per session only.

Complications

Hypotension

There were nine hypotensive episodes out of 39 DFPP sessions. There were five hypotensive episodes out of 15 DFPP sessions that used standard albumin (5%) as a replacement fluid. In four out of 24 sessions ($P = 0.12$), patients had hypotension when effluent albumin concentration was used as a replacement solution. Overall episode of hypotension during DFPP in our study was 23%. Hypotension observed when standard albumin was used as a replacement was 33.3% and when the effluent concentration of albumin was used as a replacement, it was 16.6% [Table 8].

Bleeding

Three out of 15 patients had spontaneous bleeding diathesis [Table 8]. One episode was hematochezia in a patient with a history of bleeding hemorrhoids. The second episode was hematemesis in a patient who had gastrointestinal intolerance to mycophenolate mofetil and continued on the same. The third episode was spontaneous petechiae in lower limbs with normal platelets and with minimally deranged coagulation parameters. There were no deaths. All patients with spontaneous bleeding had post-DFPP serum fibrinogen

Table 5: Fibrinogen removal

Fibrinogen	Proportional cumulative percentage removal (mean±SD)
Session 1	76±14.8 (235.6±45.9 mg/dl)
Session 2	83±8.2 (257.3±25.42 mg/dl)
Session 3	87±10.1 (269±31.3 mg/dl)
Session 4	88.4±4.2 (274.0±13.0 mg/dl)

SD: Standard deviation

Table 6: Albumin removal

Percentage of albumin removal	21.30%
Percentage of albumin removal with standard replacement	36.35%
Percentage of albumin removal with effluent concentration of albumin as replacement	11.9%
Effluent albumin concentration	1.75-2 times the serum albumin

Table 7: Plasma component removal

Plasma components	Proportional/mean removal±SD	*P* value for removal
IgG (proportional percentage mean±SD)	72±10	0.001
IgA (proportional percentage mean±SD)	89.1±4	0.001
IgM (proportional percentage mean±SD)	86.2±2.1	0.001
Calcium (mg/dl)	0.52±0.21	0.310
Phosphate (mg/dl)	0.61±0.1	0.08
Magnesium (mg/dl)	0.02±0.01	0.834
Potassium (mg/dl)	0.12±0.04	0.552
Albumin (g/dl)	0.82±0.11	0.004
Fibrinogen (proportional percentage mean±SD)	88.4±4.2	0.001
PT with INR	0.4±0.1	0.436
APTT	3.1±0.8	0.723

PT: Prothrombin time, INR: International normalized ratio, APTT: Activated partial thromboplastin time, SD: Standard deviation

Table 8: Complications

Type of complication	Percentage of complications observed
Hypotension	33.3 (standard albumin; 5/15); 16.6 (effluent albumin; 4/24)
Bleeding	20 (3/15)
Access failure	6.6 (1/15)
Others	Nil

level below 50 mg/dl. Six out of 39 sessions required plasma replacements. One patient had life-threatening bleed immediate post transplant with serum fibrinogen value of 139 mg/dl, but she also had platelet functional disorder and was on thrombopoietin supplements (thrombopoietin colony stimulating factor), and hence, it could not be completely attributed to the procedure.

Access failure

One had arteriovenous fistula failure during an episode of hypotension [Table 8].

Others

There was no episode of infection during the hospital stay, and there was no significant drop in hemoglobin or platelets postprocedure (P = 0.81 and 0.46, respectively).

Replacements

6/39 (15%) of the DFPP sessions required plasma replacements (fresh frozen plasma, cryoprecipitates). None of them required high dose IVIG for treatment. 9/39 sessions required low dose intravenous replacement immunoglobulin (100 mg/kg) and all were given post-DFPP and after the samples were taken for analysis. Replacement IVIG will not have any effect on per session removal, but it can underestimate cumulative removal. However, the rebound observed between post-DFPP values of the previous session and pre-DFPP values of successive sessions are negligible (<1%–2%).

Discussion

DFPP is a procedure, designed to selectively remove serum immunoglobulins without removing much of plasma components.[5] Since its invention by Agishi *et al*., it has been used for diverse indications, but only a few studies had analyzed the efficiency of removal of target plasma molecules and its complications.[5,6] Knowledge of the same is extremely important, as it helps to use it for appropriate indications while minimizing complications. Three studies have compared the efficiency of removal of serum immunoglobulins. Agishi *et al*. showed that there is significant removal of serum immunoglobulins, but assessment of the efficiency of removal in serial treatment sessions was not elaborated, and replacement fluids were either not used or used minimally.[5] Tanabe showed that the percentage of removal of IgM and IgG per session was 70% and 60%, respectively, with 8% albumin used as a replacement solution.[6] Hebibi *et al*., on the other hand, showed the suboptimal removal of serum IgG, IgA, IgM (37.8%, 52.8%, and 61.5%, respectively) and one of the major reasons could be not using the replacement solutions during the procedure.[7] The proportional removal efficiency in our study after the first session and after four sessions were 55% and 72% for IgG, 74% and 89% for IgA, 85% and 96% for IgM, respectively. Our results are better than Hebibi *et al.*, which can be explained by use of either 5% albumin or effluent albumin concentration as replacement solution which is roughly 1.75 – two times the serum albumin.

IgG despite being removed by DFPP in our study is still inferior compared to the available literature with conventional plasmapheresis (after first session - 63%, cumulative removal after four sessions 90%).[8] Lyu *et al*. and Tagawa *et al*., using DFPP for neurological indications also showed that the efficiency of removal of IgG[9] and anti-ganglioside antibody was inferior in DFPP in comparison with conventional plasmapheresis.[10]

These studies which have directly compared DFPP with traditional plasmapheresis have shown clear benefits for conventional plasmapheresis for removing IgG in comparison with DFPP.[9,10] This is very crucial, as it is decisive in utilizing the procedure for nonemergent conditions like desensitisation for blood group incompatible transplant, HLA allo sensitized patients prior to transplant etc., where safety is of utmost importance as against emergent conditions like antibody mediated rejection, ANCA-associated vasculitis, anti-glomerular basement membrane disease where disease is too aggressive and removal of serum immunoglobulins quickly is of utmost importance. Clearly, we will opt a safer procedure for the former indications and more effective procedure for the latter situations.

One significant observation in this study was that none of our patients had post plasmapheresis serum IgG <200 mg/dl even with lower pre plasmapheresis values between 200 and 300 mg/dl. It raises the question of efficiency of DFPP with lower serum IgG levels. The discrepancy among various studies can also be due to different baseline immunoglobulin levels and timing of initiation of plasmapheresis.[1]

However, we did not attempt to compare any correlation between immunoglobulin levels, and clinical outcome as it was very diverse population and the sample size is even more limited per disease. Furthermore, clinical outcomes of specific disease depend on disease-specific antibodies which were not the objective of this study.

Fibrinogen is another high molecular weight protein (300,000 daltons) with removal rate similar to that of IgA in our study. The efficiency of removal fibrinogen for the first session and cumulative removal at the end of four sessions were 76% and 88%, respectively. Although there was no significant change in PT with INR and APTT, individual coagulation factors have not been assessed in our study, unlike Hebibi *et al*.[7,11,12] Hanafusa *et al*. and Hebibi *et al*. clearly revealed removal of factor XIII from circulation during double filtration plasmapheresis, which will still result in normal PT with INR and requires thromboelastography or clot lysis test for detection.[11,13,14]

Removal is expressed as a proportion of percentage removal rather than an absolute number as few of the pre immunoglobulin levels are well below the mean levels and it may not be meaningful applying the same here. However, absolute values for cumulative removal are notified in the table, but we suggest an interpretation in terms of percentage will be more meaningful for the above-mentioned reason.

It's a noteworthy observation that all the patients who had spontaneous bleeding diathesis had fibrinogen levels below 50 mg/dl.

Proper spacing of DFPP is of utmost importance allowing the body to replenish fibrinogen.[15]

Sieving coefficient of albumin quoted by most manufacturers is 0.6 (Hebibi *et al.* and Agishi *et al*.). In other words, 60% of the albumin will be retained in the circulation after each DFPP session. The proportion of serum albumin removal in our study was 21.30%, with 36.35% for standard 5% albumin replacement solution and 11.9% for effluent concentration albumin used as replacement solution, respectively. Agishi *et al*. initially described the procedure without replacement solution.[5] Subsequently, many others including Tanabe started using 7.5% albumin as replacement solution which roughly contains the albumin content of 2.5 – 3 l of plasma.[6] Nishi *et al*. came up with the idea of using 12.5% albumin in which there is a significant deficiency of globulins with higher post-DFPP albumin, and there were no hypotensive episodes.[16] There is no doubt that, higher the albumin concentration, lesser will be the hypotension and as albumin is an expensive replacement solution, we hypothesized effluent albumin concentration (1.75–2.0 times the serum albumin) is a systematic way of physiologically replacing albumin in patients and may also be cost effective.

We did not find any dyselectrolytemia needing correction and the calcium replacement was given only once post procedure, unlike repeated calcium replacements during conventional plasmapheresis.

Hypotension is a complication during DFPP, which can be effectively mitigated by increasing the albumin concentration. The essential difference in episodes of hypotension among various authors is due to the varied concentration of their replacement solutions (Hebibi *et al*., and Agishi *et al*. – no replacements; Tanabe – 7.5% albumin;[6] Nishi *et al*. 12.5%;[16] our study-effluent concentration as replacements). If cost is not a consideration, opting for the highest concentration of albumin will be beneficial, otherwise, patients financial situation, frailty, and evidence shown in various studies should be the deciding factors in choosing the replacement solution. Spontaneous bleeding diathesis is rare and observed in our study only when fibrinogen is <50 mg/dl, which can be mitigated by spacing DFPP.[15]

Limitations

The sample size was small and there was no control arm with conventional plasmapheresis in our study. Nearly 15% of the patients had plasma replacements during the procedure, which may underestimate the clearance of immunoglobulins.

Conclusions

IgG, IgA, IgM, albumin, and fibrinogen are removed by DFPP. IgG is sub-optimally removed whereas IgA, IgM, and fibrinogen are substantially removed. Spontaneous bleeding diatheses are common when fibrinogen levels drops below 50 mg/dl. Hypotension can be mitigated effectively by replacing albumin based on effluent albumin concentration (1.75 – 2.0 times the serum albumin) rather than standard albumin (5%) replacement fluids.

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Conflicts of interest

There are no conflicts of interest.

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