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Teaching Point
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Membrane and centrifugal therapeutic plasma exchange: practical difficulties in anticoagulating the extracorporeal circuit

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Abstract
Therapeutic plasma exchange (TPE) is a well-established treatment modality for nephrology patients, using two conventional methods: membrane (mTPE) or centrifugal TPE (cTPE). Although the efficacy of both treatments has been described, there are few reports that compare these methodologies. Here we describe three nephrology patients who were treated with both mTPE and cTPE. The mTPE method, but not the cTPE method, was associated with persistent difficulty anticoagulating the extracorporeal circuit in all three patients. In mTPE procedures, the doses of heparin bolus and infusion rate were important determinants of whether the circuit clotted. With a heparin bolus at or below 2000 IU, clotting occurred in 67% of treatments, dropping to 25% with a bolus of >2000 IU. Likewise, a heparin infusion rate during the procedure was indicative of clotting. With a maintenance infusion of <2000 IU/h, most circuits clotted. No clotting was observed during cTPE procedures using acid citrate dextrose formula A solution as an anticoagulant of the extracorporeal circuit. Overall, difficulties maintaining the extracorporeal circuit in mTPE required the use of additional disposable sets, high doses of heparin and nursing time. In addition, mTPE procedures took longer to perform than cTPE.

Keywords: anticoagulation; centrifugal tPE; membrane tPE; therapeutic plasma exchange

Introduction

Therapeutic plasma exchange (TPE) is used for many indications in patients presenting to a variety of medical disciplines. The efficacy and safety of TPE is the subject of recent reviews [1] and guidelines from professional bodies including the American Society for Apheresis and the American Academy of Neurology. However, strong recommendations on practical aspects of the delivery of TPE are not available.

Membrane therapeutic plasma exchange (mTPE) and centrifugal therapeutic plasma exchange (cTPE) are both well-established techniques. In both, plasma is selectively removed and replaced typically with human serum albumin or fresh frozen plasma, chosen on the basis of the indication for TPE and patient clinical parameters.

There are no prospective randomized controlled trials comparing mTPE and cTPE. One uncontrolled comparison carried out >25 years ago used a cTPE device that is no longer available [2]. In another study, the complement activation was observed more frequently in the mTPE group [3].

Although apheresis registry data have been published, these do not include details of practical differences between mTPE and cTPE or the advantages of each method [4].

Between November 2010 and March 2011, we had the opportunity to evaluate mTPE and cTPE techniques at our institution. Here we describe three patients with unequivocal indications for therapeutic plasma exchange who were all treated with both mTPE and cTPE. We report practical aspects of their treatment with emphasis on reliability and safety of the techniques.

Case reports and findings

In the autumn of 2011, we had made access to both membrane TPE and a centrifugal TPE system. Our established treatment system was mTPE, but during this period we had arranged for a trial of a cTPE system. As a consequence, three patients received TPE using both mTPE and cTPE.

Exchange volumes, anticoagulation, replacement fluid employed and additional calcium supplementation used in TPE are prescribed in our unit on the basis of a written protocol (see Figure 1).

Many of the elements of this protocol of the unit were employed with the cTPE device. The main change was that exchange volumes for mTPE procedures were estimated by the prescribing physician, whereas the cTPE device calculated exchange volumes precisely according to patient parameters.

mTPE protocol

What solution to replace with: For TTP/HUS - use FFP alone

Otherwise:

Exchange with human albumin solution (HAS) 4.5% plus 0 - 30 mL of calcium gluconate 10% in 100 mL of 0.9% sodium chloride infused throughout plasma exchange, according to serum calcium:

Corrected serum calcium (mmol/l)	<2.2	2.2-2.4	2.4-2.6	>2.6
Give calcium gluconate (10%)	30 mL	20 mL	10 mL	0 mL

UNLESS:
a) pulmonary haemorrhage
b) within 5 days of renal biopsy
c) other active haemorrhage or
d) abnormal coagulation (INR or APTTKR >1.4)

In these situations use HAS 4.5%, then FFP (15 mL/kg) at the end of the exchange, plus calcium as above

Heparin: Bolus heparin should be given at a rate of up to 2000 IU for a 60kg person; 2500 IU for a 60 – 80 kg person and 3000 IU for someone over 80 kg. A maintainenance dose of 1000 to 2000 IU/hr will be required. Further boluses may be required if there is a suggestion of clotting in the circuit (filter transmembrane pressure > 100 mmHg) ACT monitoring is not available in our unit.

Blood flow: 150 mL/min

Replacement pump speed: 2000 mL/hr

cTPE protocol

What solution to replace with: For TTP/HUS use FFP alone

Otherwise:

Exchange with human albumin solution (HAS) 4.5% plus 0–30ml of calcium gluconate 10% in 100 mL of 0.9% sodium chloride infused throughout plasma exchange, according to serum calcium:

Corrected serum calcium (mmol/l)	<2.2	2.2-2.4	2.4-2.6	>2.6
Give calcium gluconate (10%)	40 mL	30 mL	15 mL	0 mL

UNLESS:
a) pulmonary haemorrhage
b) within 5 days of renal biopsy
c) other active haemorrhage or
d) abnormal coagulation (INR or APTTKR >1.4)

In these situations use HAS 4.5%, then FFP (15 mL/kg) at the end of the exchange, plus calcium as above

Exchange volume as calculated by SpectraOptia, using patient parameters:

Height: ……..……cm Weight: ……. kgs HCT: …. ……% Gender: f / m

Total Blood Volume: ……..…. mls

Plasma Volume: ……..…. mls (for treatment, round value up to the nearest 500 mls)

Blood flow: 65 mL/min

Anticoagulant Citrate Dextrose (ACD-A): 0.8 – 1.2 mls/min/L total blood volume

Observe patient for citrate toxicity (tingling, peripheral paresthesia, restlessness). If necessary, pause treatment, slow rate and give additional 10 mL Ca++ gluconate 10%.

Fig. 1. Sussex kidney unit mTPE/cTPE treatment protocols.

The mTPE device required a blood flow of 100–150 mL/min for efficient treatment but a higher blood flow did not shorten treatment duration. The cTPE device could operate with a blood flow of up to 140 mL/min, but could run as low as 5 mL/min if necessary. Higher blood flow had an immediate effect on treatment duration, as with higher flows treatment time was shortened considerably. We were advised by the manufacturer that platelet losses would be minimized (to <1%) at a blood flow of 65 mL/min, therefore we included this flow rate in our procedure protocol. Patient characteristics and treatment modalities are summarized in Table 1.

Patient 1

The first patient was a 50-year-old woman (75 kg) with acute kidney injury. Renal biopsy and antibody testing revealed anti-glomerular basement membrane disease. She was immunosuppressed with cyclophosphamide and corticosteroids and received therapeutic plasma exchange.

Table 1. Patient characteristics

Patient (age, gender, weight)	Diagnosis	Treatment	Pre-treatment result (date)	Date of last TPE	Post-treatment result (date)
1 (50, F, 75)	Crescentic glomerulonephritis with anti-GBM antibodies	CYP, MP, 12 × TPE	Anti-GBM 747 IU/mL (20 November 2010)	14 December 2010	Anti-GBM 67 IU/mL (17 December 2010)
2 (23, M, 94)	Crescentic glomerulonephritis with anti-GBM antibodies	CYP, MP, 17 × TPE,	Anti-GBM >600 IU/mL (27 January 2011)	18 February 2011	Anti-GBM 36 IU/mL (22 February 2011)
3 (57, M, 81)	ANCA-associated small vessel vasculitis	CYP, MP, 7 × TPE,	10.1 IU/mL (14 December 2010)	30 December 2010	<1.3 IU/mL (30 December 2010)

CYP, cyclophosphamide; MP, methylprednisolone; AAV, ANCA-associated vasculitis; TPE, therapeutic plasma exchange; HD, haemodialysis anti-GBM.

Table 2. Plasma exchange procedures

Patient	Type of TPE	*n*	Total heparin used during procedure (IU)	Total ACD-A infused to patient (mL)	Procedure time (min)	Time to exchange 1 L of plasma (min)
1	mTPE	5	7290 ± 3171	–	143 ± 61	44 ± 14
	cTPE	6	–	49 ± 21	104 ± 36	29 ± 5
2	mTPE	3	7750 ± 750	–	138 ± 32	34 ± 13
	cTPE	13	–	62 ± 13	116 ± 13	28 ± 4
3	mTPE	1	6300	–	160	40
	cTPE	6	–	81 ± 25	112 ± 6	28 ± 4
All patients	mTPE	9	7333 ± 2317	–	144 ± 9	40 ± 12
	cTPE	25	–	63 ± 21	112 ± 20	28 ± 4

Plasma exchange treatments (Table 2) were started with membrane filtration technology (mTPE), using the Gambro Prisma system with a TPE 2000 set (Gambro). The set was routinely primed as per policy and manufacturer's instructions with 4 L of sodium chloride 0.9%, with 5000 IU unfractionated heparin added to the last litre of fluid. Set-up and priming usually took ∼40 min.

During the first treatment, an initial heparin bolus of 1000 IU was used and the heparin infusion rate was 1000 IU/h. These doses were with 13 IU/kg lower than per protocol (33 IU/kg), as the patient had a renal biopsy the day before the exchange. At 55 min into the procedure, a rise in transmembrane pressure suggested imminent filter clotting and a further 1000 IU heparin bolus was given. Despite this, the filter clotted shortly after.

The set was changed and the patient received a further bolus of 2000 IU heparin in addition to a continued heparin infusion of 1000 IU/h. Two hours after the second bolus (time 115 min), the filter clotted again and the set was replaced for a second time. The patient received a fourth bolus of heparin (2000 IU) at 190 min and the heparin infusion rate was increased to 1500 IU/h. The third attempt to complete the exchange was uneventful but the total cumulative dose of heparin was 8750 IU. The procedure took 237 min to complete of which only 124 min were spent performing the exchange.

The patient underwent mTPE daily on the next 3 days and completion of these procedures required large heparin doses.

Altogether, four mTPE procedures were performed with one prematurely terminated because of severe clotting in the filter before the prescribed plasma exchange had been delivered. In addition, seven disposable sets were required to complete four TPE procedures. As per our treatment guidelines, the patient should have received on average of 5500 IU of heparin for a 4 L exchange but we had to use up to 9000 IU to complete TPE.

We feared that the administration of such high doses of heparin could lead to systemic anticoagulation in a patient at risk of pulmonary haemorrhage. We therefore decided to use the cTPE (Spectra Optia apheresis) device with regional citrate anticoagulation of the extracorporeal circuit.

Citrate (acid citrate dextrose formula A, ACD-A solution, 0.113 mM citrate) was infused at a rate dependent on the patient's total blood volume (TBV). In our setting, we used a rate of 0.8 mL ACD-A/min/L TBV which corresponds to between 0.0047 and 0.0068 mmol citrate/kg/min. At this rate, citrate reactions are rare. The estimated drop in ionized calcium would not be >10–15% [5].

A total of seven additional centrifugal plasma exchange procedures were performed with an average procedure time of 104 min. All seven cTPE procedures were uneventful and the prescribed dose was delivered on each occasion. In addition, the average lapsed time it took to exchange 1 L of plasma using cTPE was 29 min in contrast with 44 min using mTPE (Gambro Prisma System device).

Treatment 9 was performed with a mixture of human albumin 4.5% and FFP and cryoprecipitate using the cTPE device. This proceeded without difficulties and contrasts with our experience of mTPE where this type of exchange prescription would have proved problematic.

The patient's final TPE was delivered using mTPE and there were further difficulties with filter clotting. In total, 12 plasma exchanges were carried out, 5 mTPE and 7 cTPE. No clotting or other adverse events were observed during the cTPE procedures.

The patient's TPE was delivered using an un-tunnelled right internal jugular (RIJ) central venous catheter (CVC) during sessions 1–6 and a tunnelled RIJ CVC for sessions 7–12. Unfortunately, the patient's renal function could not be salvaged and she required long-term maintenance haemodialysis until her unrelated death at home 14 months after starting dialysis.

Patient 2

The second patient was a 24-year-old male (94 kg) with a crescentic glomerulonephritis at renal biopsy, haemoptysis and anti-GBM antibodies. He was treated with

cyclophosphamide and corticosteroids in addition to TPE. The initial treatment was delivered with mTPE. Significant problems with filter clotting were encountered despite high doses of heparin used. During the first session of mTPE, TMP started to rise after 1 h and the set clotted 25 min later. The prescribed session was completed, but a total of 7750 IU heparin was used.

A second mTPE procedure was carried out successfully without clotting but 8500 IU of heparin was needed in a patient who should have only received 6000 IU according to the local protocol.

Following these two sessions, we changed the delivery method to cTPE and 14 further procedures were carried out without problems. During the 15th procedure the patient briefly felt unwell and complained of having a metallic taste in his mouth. We speculate that this may have been due to citrate toxicity. Blood flow was decreased to 40 mL/min and an additional 20 mL of calcium gluconate was given. A normal blood flow of 65 mL/min was resumed shortly after symptoms had subsided. A final plasma exchange was delivered using mTPE, requiring a total heparin dose of 7000 IU.

The patient's TPE was delivered using an un-tunnelled RIJ CVC for sessions 1–5 and a tunnelled CVC for sessions 6–17. The patient's renal function did not recover and he received maintenance dialysis until a successful transplant 23 months after presentation.

Patient 3

The third patient was a 57-year-old man (81 kg) with ANCA-associated vasculitis, presenting with constitutional symptoms, skin, neurological and renal manifestations and bloody diarrhoea. He was treated with cyclophosphamide and corticosteroids initially and, in the absence of response to these interventions, TPE was prescribed. Six therapeutic plasma exchanges were delivered using centrifugal TPE without any problems. The fourth plasma exchange was an mTPE procedure where clotting occurred 30 min into the procedure (Heparin infusion: 1000 IU/h; bolus: 1500 IU). Heparin infusion rate was increased to 1500 IU/h, two additional boluses of 2000 IU and later on a 1000 IU bolus were given and the prescribed TPE was completed without further clotting using a new disposable set. In total, 6300 IU of heparin were given during this procedure.

The patient remained dialysis independent at the end of his course of TPE. Subsequently, his renal function declined and he started on peritoneal dialysis 15 months after his initial presentation. He remains well on this treatment 24 months after presentation.

Discussion

Therapeutic plasma exchange is a well-established treatment for renal diseases. Over a 5-month period, we had the opportunity to compare the ease of use, safety and reliability of mTPE and cTPE methods in three patients with severe renal disease. We performed 36 plasma exchange procedures on these patients, 9 using mTPE and 27 using cTPE.

The most significant observation in our study was the high frequency with which the filter clotted using mTPE with conventional heparin anticoagulation despite doses of heparin larger than advocated in our local mTPE protocol. On occasions, multiple disposable sets had to be used to complete the plasma exchange procedure, increasing procedure cost. In addition to the requirement for larger than expected doses of heparin, the mTPE procedures in this small cohort were very time consuming. mTPE took longer to set up and was more frequently complicated by the time and resource consuming need to change the extracorporeal circuit. This is problematic when expensive FFP with a limited shelf life is required for the exchange.

A heparin bolus of 50 IU/kg and an infusion rate of 1000–2000 IU/h has been used in TPE without excess clotting [6]. The protocol is also similar to that used in the Canadian series [7, 8] where a bolus of 40 IU/kg (±2800 IU) and a constant infusion rate of 20 IU/kg/h were used successfully.

In our study, the heparin bolus was somewhat higher in mTPE procedures with clotting (median: 73 IU/kg; range: 48–93 IU/kg) and without clotting (median: 48 IU/kg; range: 32–67 IU/kg). This difference was not statistically significant (Mann–Whitney *U*-test; $P = 0.37$). The heparin infusion rate was similar with clotting (median: 19 IU/kg/h; range: 13–33 IU/kg/h) and without clotting (median: 21 IU/kg/h; range: 21–27 IU/kg/h; $P = 0.12$). We can therefore conclude that clotting was not due to underdosing of heparin in these cases.

Bramlage *et al*. [9] suggest that every unit of heparin administered increased the risk for complications by ~0.3%. However, the heparin dose used in the Bramlage study at which complications started to decline, was significantly lower than that in our observations. It is highly likely that the circuit used contributes to the heparin requirement in the published observations. We also need to point out that during mTPE, antithrombin III is removed from the circuit. As a result, heparin will therefore be less effective.

In Figure 2, all findings regarding clotting are summarized. With a heparin bolus at or below 2000 IU, clotting occurred in 67% of treatments, dropping to 25% with a bolus of >2000 IU. Likewise, a heparin infusion rate during the procedure was indicative for clotting. Below 2000 IU/h, 83% of mTPE procedures clotted. At or >2000 IU/mL, this proportion dropped to 13%. In our experience of centrifugal TPE, no complications were seen apart from possible mild symptomatic hypocalcaemia in one case. Transient hypocalcaemia effects can be counteracted by giving a

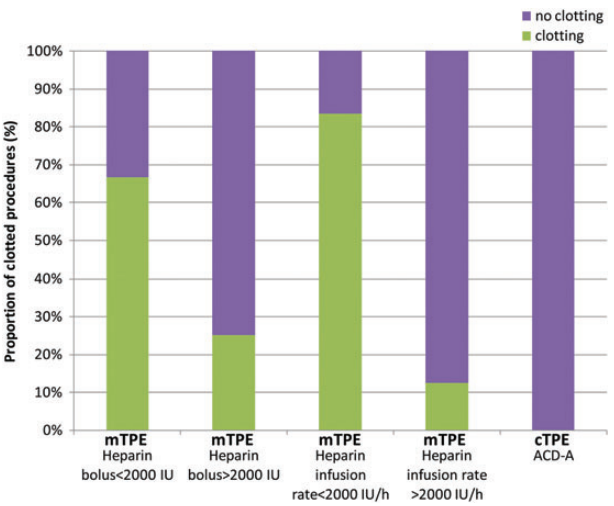

Fig. 2. Proportion of clotting in mTPE and cTPE procedures.

	cTPE (N=24)	mTPE (N=9)	p-value
Procedure time (min)	113 ± 20	130 ± 58	0.2
Time to exchange 1 L plasma volume (min)	28 ± 4	37 ± 15	0.008

Fig. 3. Procedure times.

bolus of calcium gluconate [10]. To prevent hypocalcaemia, we used a continuous calcium gluconate 10% infusion, based on pre-TPE serum calcium levels.

In two out of three patients, platelet counts fell during the series of TPE treatments. It is unclear to what extent a decline in platelet counts during a course of TPE is related to heparin exposure, bone marrow suppression secondary to therapeutic immunosuppression, platelet consumption or possibly heparin-induced thrombocytopenia. In patients with diseases which may be associated with pulmonary haemorrhage as was the case for Patients 1 and 2, it seems intuitive to avoid unnecessary heparin and reduce the risk of residual systemic anticoagulation.

No clotting was observed in the cTPE sessions where the extracorporeal circuit was anticoagulated with ACD-A. In this respect, we confirm the results of previous studies using the spectra optia apheresis device [10, 11].

Overall, the main differences in our limited clinical comparison between mTPE and cTPE are related to anticoagulation and ease of use. However, other adverse effects may be more common with mTPE. Bramlage *et al.* [9] reported an excess of adverse events using mTPE. This contrasted with adverse events observed in an earlier cTPE study in another centre [12]. Hypotension, fever, haemolysis and chills [4, 13] are described in the mTPE series in the literature [14]. A retrospective comparison of complement activation using different techniques suggested that less complement activation is seen using centrifugal methods [3].

When considering the extra costs of machine purchase and consumables for cTPE, it is worth considering the lower likelihood of clotting of the extracorporeal circuit and therefore having to use fewer consumables and expensive replacement fluids with limited shelf life after thawing.

Having taken all this into account, we have established for our unit a cost saving of consumables of £8254.40 per year when using cTPE rather than mTPE. There are in addition variable savings on blood products through reduced waste. The impact of increased procedure time, set-up time and treatment duration on nursing resources should also be taken into account (Table 2 and Figure 3).

In addition, even though we used central access on the patients reported, the centrifugal device also has the advantage that it can be used with peripheral access and also operates in single needle mode.

We have used the device on a neurological patient with peripheral access without problems. Blood flow was somewhat slower with 40–60 mL/min and procedure time accordingly somewhat longer, but we could not have treated this patient with our membrane device, as this needed a blood flow of at least 100 mL/min. This would not have been achievable with peripheral access in this case.

Teaching points

(i) Centrifugal TPE with citrate anticoagulation is an alternative to membrane-based TPE and heparin anticoagulation.
(ii) Membrane-based TPE may require substantial doses of heparin to anticoagulate the extracorporeal circuit.

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Conflict of Interest statement. None declared.

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