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Effectiveness and safety of regional citrate anticoagulation for membrane-based therapeutic plasma exchange in the intensive care

Simon Klein

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2018

**EFFECTIVENESS AND SAFETY OF REGIONAL CITRATE ANTICOAGULATION
FOR MEMBRANE-BASED THERAPEUTIC PLASMA EXCHANGE IN THE
INTENSIVE CARE**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Par **Simon KLEIN**
[Données à caractère personnel]

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Mikhail Boulgakov, Récit d'un jeune médecin.

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Annals of Intensive Care, 2017, 7(Suppl 1): P167

Ce travail est en cours de soumission dans une revue médicale.

Résumé

Objectifs : Evaluer la sécurité et l'efficacité d'une anticoagulation régionale au citrate lors de la réalisation de séances d'échange plasmatique par filtration en réanimation.

Schéma de l'étude : Etude observationnelle rétrospective

Modalités : Unité de Réanimation Polyvalente de 18 lits

Population : Cohorte rétrospective incluant tous les patients traités par échange plasmatique utilisant une technique de filtration entre Avril 2013 et Juillet 2016

Interventions : Aucune

Mesures et résultats principaux : L'objectif principal de l'étude est d'étudier l'incidence de survenue d'une thrombose de filtre. Les objectifs secondaires comprennent le recueil des effets secondaires propres aux séances d'échange plasmatique et l'évaluation de la tolérance de l'anticoagulation régionale au citrate. Deux cent soixante séances d'échange plasmatique par filtration, réalisées chez 24 patients, ont été incluses dans notre étude. Le score IGS II moyen des patients était de 32 ± 17 . Les principales indications thérapeutiques étaient représentées par les microangiopathies thrombotiques ($n = 12, 50\%$). Durant chaque séance, environ une fois et demie le volume plasmatique estimé était traité. Pour chaque première séance, un protocole initial à débit fixe a été utilisé chez les différents patients. Un total de 29 séances (11.2%, 95% CI 7.3 - 14.8) réalisées chez 10 patients ont été compliquées d'une thrombose de circuit. Aucun des paramètres propres aux patients n'était corrélé au risque thrombotique. Un plus grand volume de liquide de substitution (4079 ml vs 3882 ml, $p = 0.01$), ainsi que des changements plus fréquents des vitesses de substitution (24% vs 6.5%, $p = 0.004$) ont été observés dans les séances compliquées de thrombose de filtre. Des effets secondaires mineurs, sans menace sur le pronostic vital, ont été relevés chez 7 patients (29 %) lors de 11 séances (4.2 %). Aucun

désordre métabolique notable en lien avec l'anticoagulation au citrate n'a été rapporté. Une baisse moyenne du calcium ionisé de 0.11 ± 0.12 mmol/l a été relevée lors des séances d'échange plasmatique.

Conclusion : Il semble que l'anticoagulation régionale au citrate lors de séances d'échange plasmatique par filtration chez des patients de réanimation soit une technique efficace et sûre.

Mots Clés : Anticoagulation régionale au citrate ; échange plasmatique membranaire ; réanimation ; thrombose de filtre ; microangiopathie thrombotique ; circulation extra corporelle

Abstract

Objective: To evaluate the effectiveness and safety of regional citrate anticoagulation (RCA) in membrane-based plasma exchange (mTPE) therapy for ICU patients.

Design: Retrospective observational study

Setting: 18-bedded adult intensive care unit

Patients: Retrospective cohort of all patients receiving mTPE between April 2013 and July 2016

Interventions: None

Measurement and Main Results: The primary endpoint was the occurrence of circuit clotting. Secondary endpoints were the safety of plasma exchange, and tolerance of RCA. Two hundred and sixty mTPE sessions performed in 24 patients were included. Mean SAPS 2 score was 32 ± 17 . Thrombotic microangiopathy ($n = 12, 50\%$) was the commonest indication for mTPE. During each session, 1.5x the total estimated plasma volume was exchanged. A fixed rate protocol was employed for the first session of each patient. A total of 29 treatments (11.2%, 95% CI 7.3 - 14.8) performed in 10 patients were complicated by circuit clotting. Clotting risk was not related to patient characteristics. A larger substitution volume (4079 ml vs 3882 ml, $p = 0.01$) and more frequent changes in calcium substitution (24% vs 6.5%, $p = 0.004$) were observed during the sessions where thrombosis occurred within the circuit. Adverse clinical events (but no major complications) were noted in 7 patients (29 %) during 11 sessions (4.2 %). Metabolic parameters were not-significantly altered by RCA. Mean plasma ionized calcium (iCa) decreased during RCA by 0.11 ± 0.12 mmol/l.

Conclusion: Regional citrate anticoagulation appears to be an effective and safe choice for membrane based therapeutic plasma exchange in the intensive care setting.

Keywords: Regional citrate anticoagulation ; membrane-based plasma exchange ; intensive care unit ; circuit thrombosis ; thrombotic microangiopathy ; extracorporeal circulation

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Article

Abbreviation list

TPE: Therapeutic plasma exchange

FFP: Fresh frozen plasma

RRT: Renal replacement therapy

ASFA: American society for apheresis

TTP: Thrombotic thrombocytopenic purpura

cTPE: Centrifugal based therapeutic plasma exchange

mTPE: Membrane based therapeutic plasma exchange

ICU: Intensive care unit

RCA: Regional citrate anticoagulation

ACD-A: Dextrose citrate solution A

iCa: Ionized calcium

SAPS II: Simplified acute physiology score II

1. Introduction

Therapeutic plasmatic exchange (TPE) is a blood purification technique consisting of the separation, removal and replacement of a large amount of plasma by substituting a fluid, such as fresh frozen plasma (FFP) or human albumin. The main therapeutic goal is removal of suspected pathogenic proteins (antibodies, immune complexes) or the supply of certain deficient factors (ADAMTS 13, complement fraction). TPE differs from other blood purification techniques such as renal replacement therapies (RRT) because it removes large molecular weight substances ($> 15,000$ Da). According to the therapeutic guidelines published by the American Society for Apheresis (ASFA) in 2016 [1,2], thrombotic thrombocytopenic purpura (TTP), pulmonary renal syndrome and hyperviscosity syndrome are all considered as emergency indications for apheresis in ICU.

Two separation methods (**figure 1**) involving different physical principles are used to achieve TPE. Blood components can be separated by centrifugal force according to density (cTPE) or separated by a highly permeable membrane according to molecular size (mTPE, **figure 2**). Both techniques are reported to be equally efficient for blood purification [3]. The centrifugal method (cTPE) requires specific devices generally limited to nephrology or transfusion units. Membrane-based TPE (mTPE) can be carried out with standard hemofiltration machines, which are widely available in ICUs. Interest for this method of TPE has gained momentum over recent years [4].

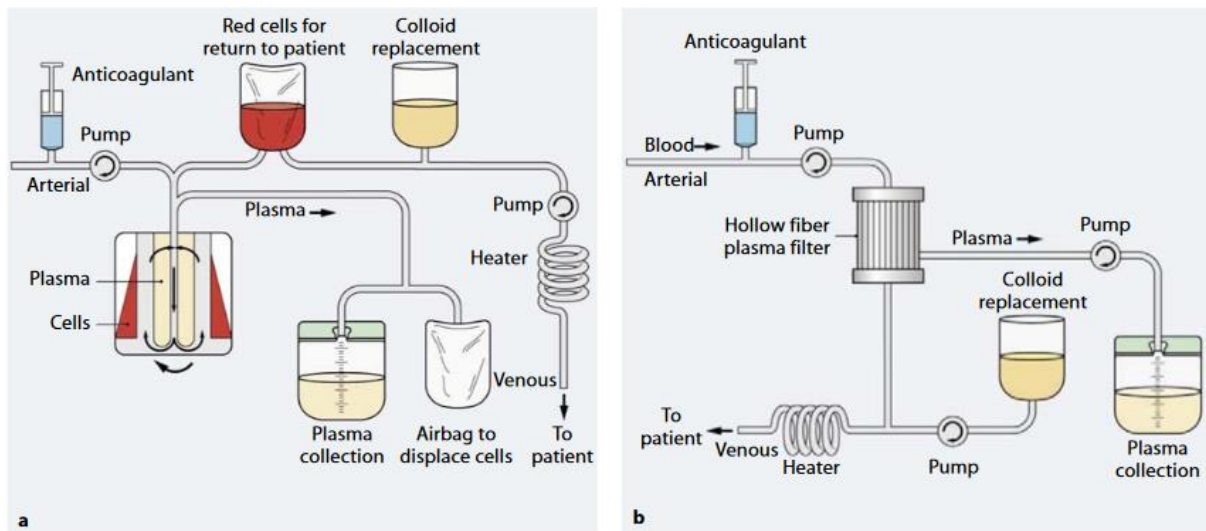


Figure 1 - Plasma exchange techniques. Comparison of cTPE (a) and mTPE (b) circuit. From [5]

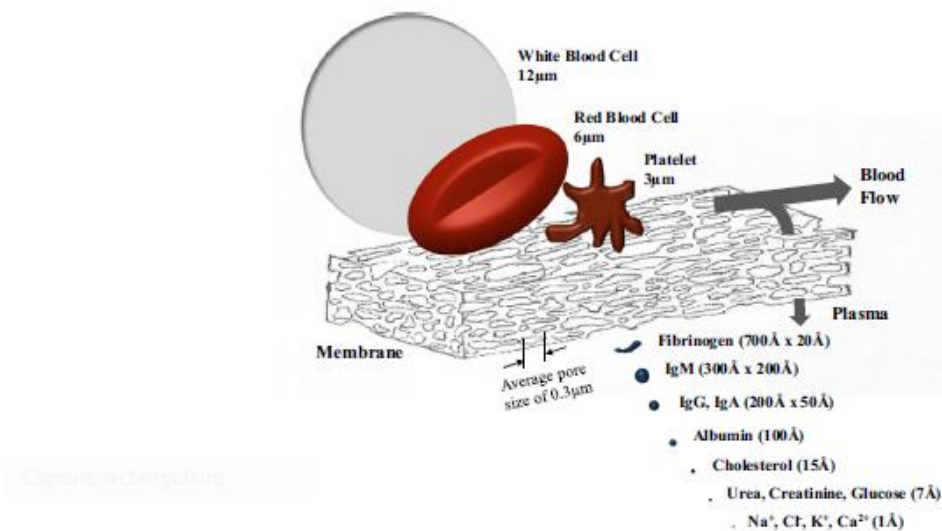


Figure 2 - Schematic of a membrane plasma separator with comparative sizes of blood cellular components and plasma constituents. From [4]

Anticoagulation of the extracorporeal circuit is essential to extend circuit life and preserve filter performance. Regional citrate anticoagulationⁱ in mTPE has already been described in various clinical contexts [6,7] but data for ICU patients remains scarce [8,9]. Systemic heparin anticoagulation remains the preferred choice for mTPE in most patients. This type of anticoagulation is however associated with risks of bleeding and heparin-induced thrombocytopenia. Regional citrate anticoagulation (RCA) is one possible alternative. Citrate anticoagulation is considered to be challenging due to the risk of complications from citrate accumulation [10,11]. Although some physicians are still reluctant to switch to RCA for mTPE, intensivists have acquired clinical experience in the use of RCA due to its application in renal replacement therapy since the late 2000s. RCA has become the standard of care for this indication [12] because it ensures longer filter life and is associated with less systemic bleeding complications and reduced platelet accretion [13] . Survival benefits remain unproven [14].

RCA became the routine anticoagulation procedure for mTPE in the Chambéry Hospital ICU in April 2013. The aim of the present study was to present the retrospective data and subsequently evaluate the effectiveness and safety of RCA for mTPE in the ICU population.

2. Patients and Methods

Ethical approval for the study was obtained from the regional ethics committee (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

2.1 *Study design*

This was a retrospective observational study to evaluate the use of RCA in mTPE in an adult general intensive care unit. All consecutive patients receiving mTPE with RCA in the Metropole-Savoie Hospital ICU (Chambery, France) from April 2013 to July 2016 were included. Patients were identified from the hospital administrative database and data concerning TPE sessions were extracted from the patient files. TPE sessions were excluded if performed without RCA or if data was incomplete.

2.2 *Technique*

Membrane-based TPE was undertaken with a Prismaflex machine (Baxter, Germany) and TPE 2000 plasma filter (Baxter/Gambo). Indication of treatment were limited to category I and II patients' according to ASFA guidelines. One and half estimated plasma volume was exchanged during each session. Initial treatments were performed daily or every second day depending on the clinical indication. All patients had central venous access. With the Prismaflex system on pre-set TPE-mode, the circuit was primed according to manufacturer's recommendations. Initial blood flow was set at a fixed rate of 150 ml/min and the fluid substitution flow rate at 2000 ml/h for the first treatment of each patient (estimated filtration fraction of 23 %). Regional anticoagulation was achieved using an infusion of dextrose citrate solution A (ACD-A, 113 mmol/l, 3% citrate, MacoPharma, France) connected to the arterial

line of the circuit (initial infusion rate 360 ml/h equating to 4.4 mmol/l of whole blood). Calcium chloride solution (10% CaCl₂) was infused into the distal end of the venous line at an initial rate of 20 ml/h (0.8 mmol/L of whole blood). Calcium infusion rate was subsequently modified to maintain plasma iCa within physiologic range (1.1 to 1.3 mmol/l). Arterial iCa was monitored at baseline and one hour after commencing the session. Arterial blood samples (blood gases, haematocrit, iCa) were analysed using a bedside RAPIDPoint© 500 (Siemens, Germany) automated device. Baseline electrolytes (sodium, potassium, calcium) were analysed in the laboratory. Vital signs were recorded every 15 minutes during the session.

2.3 *Endpoints*

The primary endpoint was the effectiveness of citrate anticoagulation as evaluated by the occurrence of circuit clotting. Secondary end points were safety-related, namely the incidence both side effects from RCA and general adverse events (AEs) from mTPE. Poor tolerance to citrate was defined as the presence of: severe hypocalcaemia (iCa < 1.0 mmol/l), severe acidosis (pH < 7.30), severe alkalosis (pH > 7.50).

2.4 *Statistical analysis*

Qualitative data, presented as numbers and percentages, were compared using a chi-squared or Fisher test as appropriate. Quantitative data are presented as mean value and standard deviation (mean ± SD). Differences between groups were evaluated by non-parametric tests (Mann-Whitney) using Statview software, with p < 0.05 considered statistically significant.

3. Results

3.1 Study population

A total of 283 mTPE sessions were performed in 26 patients during the study period. Of these, 260 sessions (performed in 24 patients) were retained for final analysis (**figure 3**). Twenty-one sessions were excluded because of incomplete data, the remaining 2, due to the use of heparin. The mean number of sessions per patient was 11 ± 12 (range 2-57).

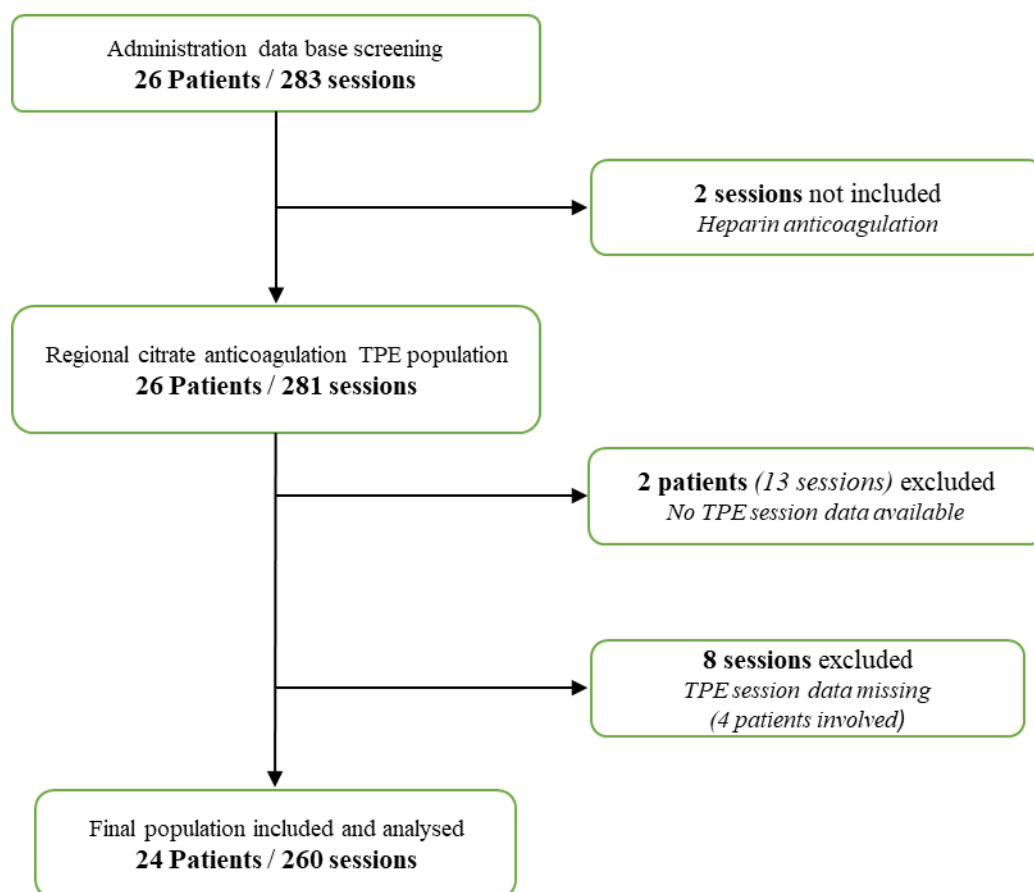


Figure 3 - Flow chart of the study population. ICU: Intensive Care Unit. TPE: Therapeutic Plasma Exchange.

The principal patient characteristics are shown in **table I**. Mean SAPS 2 score was 32 ± 17 . Of the outliers ($n = 8$), of them (17% all patients) had a SAPS 2 score < 10 : this group represents those only admitted in ICU to perform mTPE. The 4 patients with an elevated SAPS 2 score (> 50) were critically ill. Four patients died. Sixteen patients (61%) required at least one life-sustaining treatment (invasive or non-invasive ventilation, catecholamine vasopressors or RRT) during their stay in the ICU. Indications for treatment were limited to those patients defined in category I and II of the ASFA guidelines. Thrombotic microangiopathy ($n = 12$, 50%) was the commonest indication, the underlying diseases being thrombotic thrombocytopenic purpura ($n = 4$) or haemolytic uremic syndrome ($n = 8$). Additional thrombotic risk factors were identified in 8 patients, 6 of whom had underlying malignancy, the remaining 2 were pregnant.

Table I – Characteristics of patients

Number of patients	24
Age (years)	57 ± 20
Female sexe	12 (50%)
SAPS2 score	32 ± 17
Comorbidity	
Cancer history	6 (25%)
Supportive therapies	
Vasopressor	4 (17%)
Mechanical ventilation	8 (33%)
Non-invasive ventilation	4 (17%)
Renal replacement therapy	7 (29%)
Number of TPE sessions per patient	11 ± 12
Indications for TPE	
Thombotic microangiopathy (TTP / HUS)	12 (50%)
Pneumorenal syndrome and glomerulonephritis	6 (25%)
Polyradiculonevritis and myasthenia gravis	3 (12.5%)
Miscellaneous ¹	3 (12.5%)

TTP: thrombotic thrombocytopenic purpura. HUS: haemolytic uremic syndrome.

SAPS 2: simplified acute physiology score.

Results are expressed as mean \pm standard deviation and as number of patients with percentage in parenthesis.

¹Cryoglobulinemia, multiple sclerosis, hyperviscosity syndrome

3.2 *mTPE technique*

Replacement fluid consisted of FFP in 158 (61%) sessions, FFP and 4% albumin in 45 (17%) sessions, 4% albumin and starch in 38 sessions (15%) and 4% albumin in the remaining 19 (7%). The mean duration of a TPE session was 120 ± 17 min. Mean blood flow was 152 ± 9 ml/min while mean fluid substitution rate was 1947 ± 168 ml/h. ACD-A was infused at a mean rate of 312 ± 107 ml/min with the prescribed rate being 360 ml/h in 189 (73%) sessions. Mean ionized calcium in the circuit, measured in a third of the sessions, was 0.44 ± 0.22 (IQR 0.20 – 0.97) mmol/l.

3.3 *Effectiveness of RCA*

Formation of thrombosis (clotting) within the circuit occurred in 29 mTPE treatments (11.2%, 95% confidence interval 7.3 – 14.8%). Circuit clotting involved 10 (42%) patients. Sessions were continued after changing the disposable circuit tubing set in all but 3 (1.2%) cases. Circuit thrombosis recurred in the second tubing set in 3 (11.5%) cases.

3.4 *Factors associated with failure of RCA*

Circuit clotting was not associated with any specific patient characteristic (**table II**). A larger substitution volume infusion (4079 ml vs 3882 ml, $p = 0.01$) and more frequent changes in calcium substitution (24% vs 6.5%, $p = 0.004$) were observed during sessions complicated by circuit thrombosis (**table III**). No significant difference in haematocrit or pre-treatment calcium was detected between patients affected by circuit clotting and those unaffected. No clotting occurred in any session where 4% albumin and starch were used for fluid substitution.

Table II - Comparison of patients' characteristics according to thrombosis complications.

	Thrombosis (n = 10)	No thrombosis (n = 14)	P value
Age (years)	45,4 ± 18	58,2 ± 17,8	0,09
Female sexe	4 (40%)	8 (57%)	0,68
SAPS2 score	25,1 ± 12,4	36,8 ± 19	0,09
Comorbidity			
Cancer history	2 (20%)	4 (29%)	0,99
Supportive therapy			
Vasopressors	0 (0%)	4 (29%)	0,11
Mechanical ventilation	2 (20%)	6 (43%)	0,39
Non-invasive ventilation	1 (10%)	3 (21%)	0,61
Renal replacement therapy	3 (30%)	4 (29%)	0,99
Number of sessions per patient	13 ± 17	9,4 ± 6,7	0,95

SAPS2 score : simplified acute physiology score

Results are expressed as mean ± standard deviation (SD) and as number of patients with percentage in parenthesis

Table III - Comparison of sessions according to thrombosis complications

	Thrombosis	No thrombosis	P value
Hematocrit (%)	0,27 ± 0,04	0,28 ± 0,06	0,47
Blood flow (ml/min)			
prescribed	156 ± 14,7	152 ± 8,1	0,005
maximum	155 ± 14	153 ± 11,2	0,14
Total reinjection volume (ml)	4079 ± 405	3882 ± 625	0,01
Maximum reinjection flow (ml/h)	1983 ± 93	1943 ± 175	0,23
Calcium flow prescribed (ml/h)	17,6 ± 5,1	17,3 ± 4,1	0,37
Calcium flow change (%)	7 (24%)	15 (6,5%)	0,004
Maximum ACD-A flow (ml/h)	308 ± 118	312 ± 102	0,96
Pre-treatment total calcium (mmol/l) ¹	2,19 ± 0,16	2,30 ± 0,24	0,09
Pre-treatment ionized calcium (mmol/l) ²	1,22 ± 0,05	1,20 ± 0,11	0,5
Substitution fluid			
including fresh frozen plasma	26 (90%)	177 (87%)	0,15
only with fresh frozen plasma	16 (55%)	142 (61%)	0,55
albumin and starch	0 (0%)	38 (16%)	0,01
only with albumin	3 (10%)	16 (7%)	0,45

ACD-A : Anticoagulant Citrate Dextrose Solution A. ¹ n = 186. ² n = 89.

Results are expressed as mean ± standard deviation and number of patient with percentage in parenthesis.

3.5 *Safety of treatment*

Adverse clinical events were observed in 7 (29%) patients during 11 (4.2 %) sessions; urticaria (1 session each for 2 patients), well-tolerated arterial hypertension (4 sessions in the same patient), mild bradycardia (1 session each for 2 patients), paraesthesia without metabolic abnormality (2 sessions in the same patient) and one haemothorax during internal jugular catheterization. One patient with neurological involvement of TTP and a do-not-resuscitate order became comatose and died during mTPE. Cerebral haemorrhage was suspected but not confirmed by any investigation.

Bleeding at the puncture site of vascular access was observed in one patient between TPE sessions. Catheter dysfunction occurred in 5 sessions (1.9%), requiring catheter replacement in 3 cases. One case of suspected catheter-related infection was reported.

As shown in **table IV**, metabolic parameters were not significantly altered by RCA. Measurement of plasma ionised calcium before and during RCA was available for 42 sessions: mean iCa decreased from 1.19 ± 0.12 to 1.08 ± 0.13 mmol/l, representing a mean decrease of 0.11 ± 0.12 mmol/l. Severe asymptomatic hypocalcaemia (iCa < 1.0 mmol/l) was observed during 10 sessions, including 3 patients with iCa below 0.75 mmol/l. Maximum blood flow was slightly significantly higher during these sessions (155 ± 16 ml/min vs 150 ± 0 ml/min, p 0.01) whereas ACD-A infusion rates (290 ± 103 ml/h vs 322 ± 93 ml/h, p 0.35) and fluid substitution rates (1900 ± 211 ml/h vs 1948 ± 163 ml/h, p 0.34) were similar. Severe asymptomatic hypocalcaemia (iCa < 1.0 mmol/l) was observed after 8 sessions, including one patient with iCa below 0.75 mmol/l. TPE parameters in these sessions did not differ from parameters in sessions without severe hypocalcaemia (data not shown).

Table IV - Metabolic parameters related to regional citrate anticoagulation.

	Baseline (t'0)	Per-treatment (t60min)	End
Systemic iCa (mmol/l)	1,20 ± 0,10 (n = 83)	1,12 ± 0,12 (n = 72)	1,20 ± 0,17 (n = 73)
pH	7,44 ± 0,05 (n = 85)	7,43 ± 0,08 (n = 44)	7,41 ± 0,07 (n = 30)
Base Excess	4,0 ± 4,9 (n = 96)	n/c	4,1 ± 6,4 (n = 43)
HCO ₃ ⁻ (mmol/l)	27,03 ± 4,7 (n = 191)	n/c	26,5 ± 5,2 (n = 63)

iCa : ionized calcium. N/c : not calculated.

Results are expressed as mean ± standard deviation and number of patient with percentage in parenthesis

Arterial pH was measured during 44 sessions. Severe acidosis (pH < 7.30) was documented in 3 patients, of whom 2 developed lactic acidosis during TPE (pH falling from 7.38 to 7.08 and from 7.45 to 7.23 respectively). Severe alkalosis (pH > 7.50) was documented in 4 patients, including 2 with pre-existing alkalosis (pH 7.46 and 7.53 respectively).

Arterial pH was measured after 30 sessions. There were 3 cases of severe acidosis (2 respiratory acidosis, 1 lactic acidosis) and 4 cases of severe alkalosis. One patient with alkalosis was alkalotic before (pH 7.46), during (pH 7.47) and after mTPE (pH 7.52).

4. Discussion

Data concerning anticoagulation in ICU-based TPE has been limited to date since this treatment modality is currently used in less than 3% of all patients [9]. Protocols for TPE also vary from one country to another [15]. This retrospective study shows that regional citrate anticoagulation is not only technically feasible for mTPE but in addition, seems an effective and safe option. It is one of the first reports on the use of RCA for mTPE in the intensive care population.

The 11.2% incidence of circuit clotting during mTPE in our cohort falls within the acceptable range (7.3% – 15.5%) reported in the literature [6,8]. A greater incidence (up to 22.8%) of circuit thrombosis has been reported in ICU patients [9]. Aside from premature cessation of the treatment with its ensuing consequences, circuit failure due to clotting increases procedure time and demands more nursing resources and additional costs. Membrane-based TPE, like other convective techniques, is inherently associated with the challenges of circuit anticoagulation. Using systemic heparin anticoagulation, circuit clotting has been shown to occur more frequently in mTPE than cTPE (83% vs 67% with heparin bolus < 2000 IU, 25% vs 13% with heparin infusion rate > 2000 IU/h) [16]. However, it is important to note that the rheological conditions of these two TPE techniques are very different owing to the physical principles used to separate the blood components. No circuit clotting has been observed in cTPE with RCA in a limited number of studies [17,18]. To our knowledge, no study has yet compared the use of heparin and regional citrate anticoagulation in mTPE.

Patency of the extracorporeal mTPE circuit is not only dependent on adequate circuit anticoagulation. Biocompatibility and membrane characteristics are other important factors to be considered when using filtration techniques. The initial estimated filtration fraction in our fixed TPE protocol was below the target of 25% recommended to minimize the procoagulant

effect of haemoconcentration. Furthermore, the citrate infusion was administered before the filter as a predilution strategy to improve downstream rheology. It is also conceivable that the presence of citrate and hypocalcaemia within the circuit may exert a beneficial anti-inflammatory effect [19], notably in diseases with qualitative platelet dysfunction such as TTP. Risk of circuit clotting in mTPE could be aggravated by disease-related factors. Although illness severity scores are rarely mentioned in studies involving non-ICU patients, clotting complications may be more frequent in critically-ill patients with hemodynamic instability, renal impairment and/or an intense systemic inflammatory response.

No life-threatening complications or major citrate-related adverse effects were seen. Mild hypotension or hypertension, fever and shivering during mTPE have been described to occur in a minority of cases in the literature [6,20]. Recent analysis of the World Apheresis Association registry [21] suggests that adverse events are more likely to occur in mTPE than cTPE (11% vs 6%, p-value < 0.0001, OR 1.8, CI: 1.5–2.3) regardless of the type of anticoagulation used. We observed good tolerance of RCA in this study, a finding corroborated by previous authors [6,20]. Citrate-induced metabolic disorders with RCA are complex, since both citrate solution and substitution fluid can influence acid-base status [22,23]. Metabolic alkalosis is often described after repeated apheresis procedures, and appears to be exacerbated by the use of FFP [24] and citrate in patients with acute kidney injury. Citric acid is known to undergo hepatic metabolism with the release of sodium bicarbonate. The pH of the 4 patients with severe metabolic alkalosis normalised spontaneously after completion of the mTPE procedure, most likely consistent with a temporary net overload of citrate. No patient required additional haemodialysis for metabolic disturbances. As previously reported with the use of RCA in continuous RRT (CRRT), metabolic changes are generally mild [25]. Metabolic

monitoring is however essential to detect any metabolic disturbances with potential clinical repercussions.

Compared with CRRT, mTPE treatments are shorter, intermittent and rarely concern patients with hepatic dysfunction. Inadequate calcium supplementation seems to be more important than citrate accumulation in mTPE. Systematic pre-treatment measurement of iCa and routine calcium supplementation during the procedure [26] are two steps that help to minimise the risk of severe citrate-induced hypocalcaemia.

The value of measuring iCa within the circuit as a means of assessing adequacy of anticoagulation remains unclear. In addition, no clear recommendations exist about sample timing or the concentration of iCa to be targeted. Our mTPE protocol, similar to RRT techniques, used a fixed citrate dose without routine measurement of iCa in the circuit. Mean circuit iCa monitored at the discretion of the treating intensivist (82 sessions, 32%) was 0.44 ± 0.22 mmol/l. Other authors [7] have proposed to individualize the dose of citrate using an approach based on haematocrit and pre-treatment calcium level. Neither of these parameters was associated with circuit clotting in our study. It is of interest to note that the same group observed circuit clotting in 10.5% of sessions and severe hypocalcaemia in 8.5% (both figures comparable to our results) despite maintaining circuit iCa within the target range (0.24 – 0.33 mmol/l). Schwarzer et al [27] has questioned the reliability of measuring such low concentrations of iCa with blood gas analysers.

Two technical limitations of the mTPE treatments undertaken in our ICU merit discussion. Firstly, the absence of an integrated calcium and citrate delivery system [28] carries a theoretical risk of uncontrolled citrate infusion in case of a malfunction in the main pump or calcium syringe-driver. Betz et al. developed a protocol for an RCA module integrated into a hemofiltration circuit in order to address this problem [6]. Secondly, the total volume infused

(substitution fluid and citrate solution) can result in hypoalbuminemia if multiple TPE treatments are used [29]. Reducing the volume of citrate infused by administering a more concentrated citrate solution would be one option for counteracting this problem. Theoretically, such a solution could also improve the effectiveness of TPE by rendering the blood less dilute and reducing fluid overload. Antonic et al [20] demonstrated a reduced fluid load with the use of a 15% citrate solution but failed to show any difference in TPE efficacy.

5. Conclusion

Membrane-based TPE can be carried out with standard hemofiltration machines, which are widely available in intensive care units. Data concerning anticoagulation in ICU-based mTPE has been limited to date. This retrospective study shows that regional citrate anticoagulation is not only technically feasible for mTPE but in addition, seems an effective and safe option. The 11.2% incidence of circuit clotting during mTPE in our cohort falls within the acceptable range (7.3% – 15.5%) reported in the literature. Metabolic parameters were not significantly altered by regional citrate anticoagulation. Severe asymptomatic hypocalcaemia ($iCa < 1.0$ mmol/l) was observed after 8 sessions. The pH of the 4 patients with severe metabolic alkalosis normalised spontaneously after completion of the mTPE procedure, most likely consistent with a temporary net overload of citrate. No patient required additional haemodialysis for metabolic disturbances. No major clinical adverse events were noted during mTPE session.

Future comparative studies should be envisaged to explore the advantages of citrate versus heparin. Whether an individualized dose of citrate is superior to a fixed dose remains to be established.

TITRE :

EFFECTIVENESS AND SAFETY OF REGIONAL CITRATE ANTICOAGULATION FOR MEMBRANE-BASED THERAPEUTIC PLASMA EXCHANGE IN THE INTENSIVE CARE

Conclusion

Membrane-based TPE (mTPE) can be carried out with standard hemofiltration machines, which are widely available in intensive care units (ICU). Data concerning anticoagulation in ICU-based therapeutic plasma exchange has been limited to date. This retrospective study shows that regional citrate anticoagulation is not only technically feasible for mTPE but in addition, seems an effective and safe option. The 11.2% incidence of circuit clotting during mTPE in our cohort falls within the acceptable range (7.3% – 15.5%) reported in the literature. Metabolic parameters were not significantly altered by regional citrate anticoagulation. Severe asymptomatic hypocalcaemia ($iCa < 1.0$ mmol/l) was observed after 8 sessions. The pH of the 4 patients with severe metabolic alkalosis normalised spontaneously after completion of the mTPE procedure, most likely consistent with a temporary net overload of citrate. No patient required additional haemodialysis for metabolic disturbances. No major clinical adverse events were noted during mTPE session.

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VU ET PERMIS D'IMPRIMER
Grenoble le : 15/06/2018

**LE DOYEN
DE L'UFR DE MEDECINE**

Pr. Patrice MORAND

Le Doyen de l'UFR de Médecine

Pr. Patrice MORAND

LE PRÉSIDENT DU JURY

Pr. Jean François PAYEN



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Notes

¹Regional citrate anticoagulation. Adapted from *Renal intensive care self-learning module* published by Gambro®.

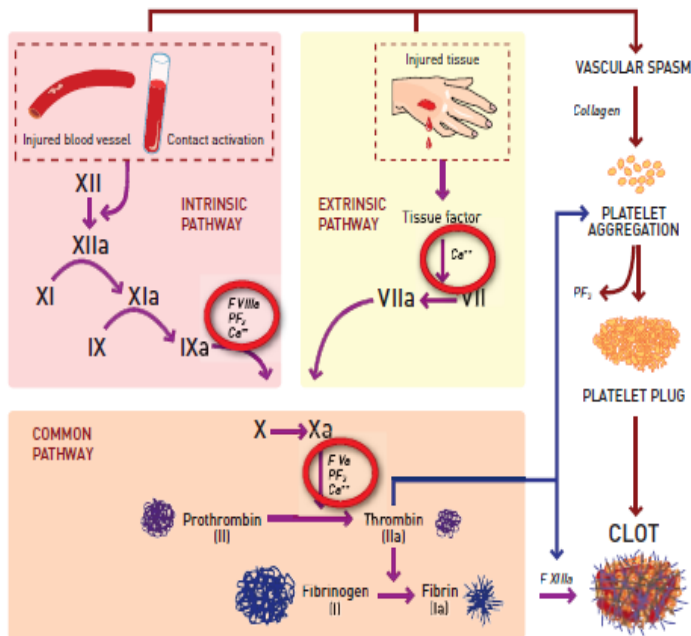


Figure 4 - Role of calcium in coagulation cascade

Calcium is required for the generation of thrombin at several level during the coagulation cascade.

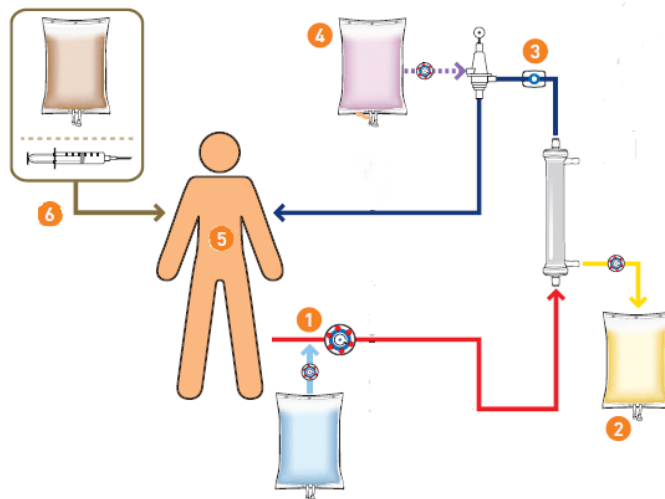


Figure 5 - Overview of citrate anticoagulation.

- (1) Citrate is infused in the arterial line of the circuit to chelate ionized calcium, and thus preventing thrombus formation.
- (2) Calcium-citrate complex are partially removed by filtration membrane.
- (3) Filter ionised calcium can be monitored to assess anticoagulation status.
- (4) A substitution/replacement fluid is used.
- (5) The remaining citrate is rapidly metabolized by the mitochondrial citric acid cycle in liver, kidney and muscle.
- (6) Calcium loss must be compensated with calcium infusion.

Tableaux

Table I - Characteristics of patients

Table II - Comparison of patients' characteristics according to thrombosis complications.

Table III - Comparison of sessions according to thrombosis complications

Table IV - Metabolic parameters related to regional citrate anticoagulation.

Figures

Figure 1 - Plasma exchange techniques. Comparison of cTPE and mTPE circuit.

Figure 2 - Schematic of a membrane plasma separator.

Figure 3 - Flow chart of the study population.

Figure 4 - Role of calcium in coagulation cascade

Figure 5 - Overview of citrate anticoagulation

ANNEXES

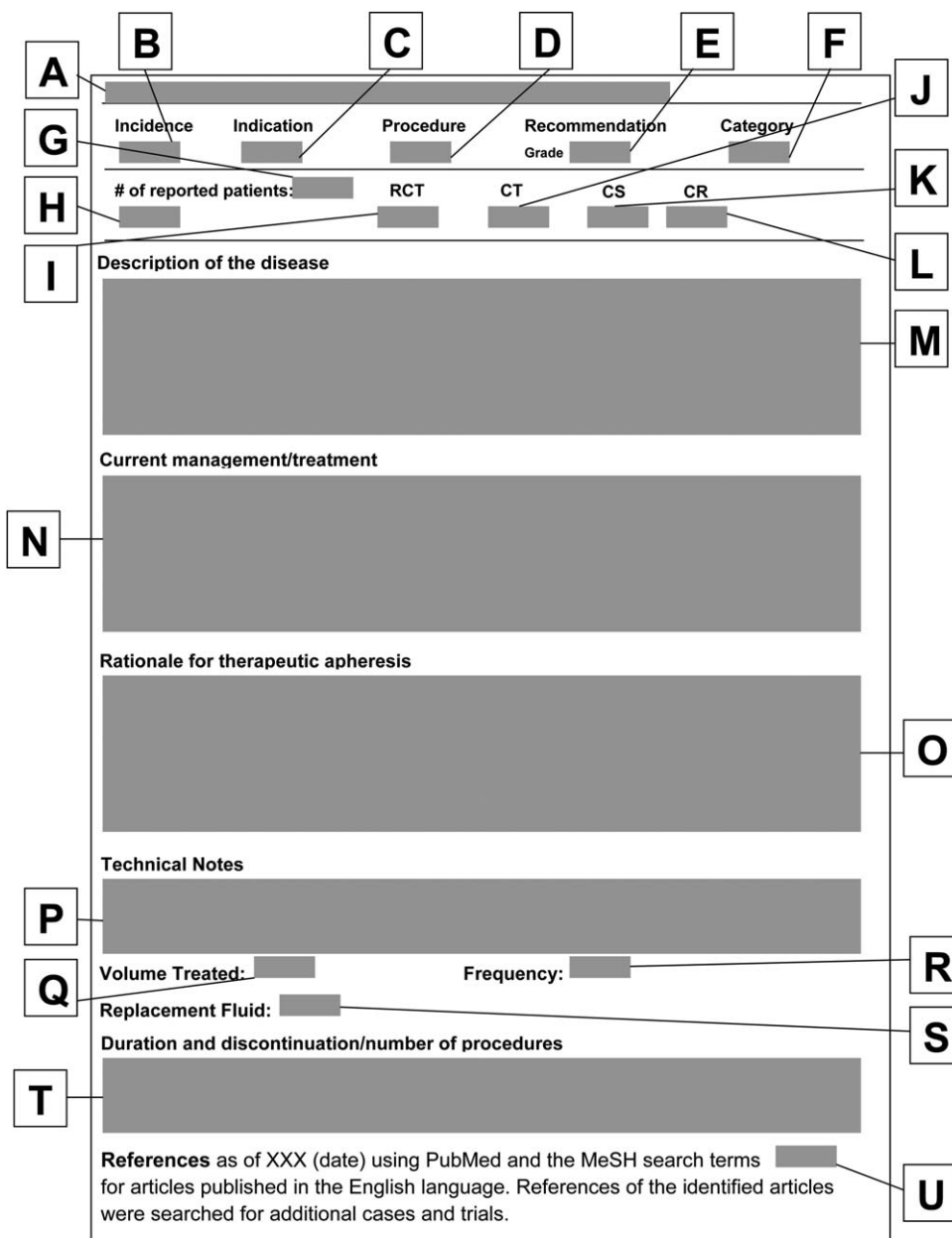


Fig. 1. Explanation of the fact sheet used in the ASFA Special Issue, Seventh Edition (2016).

- A The name of the disease as well as its eponym when appropriate.
- B This section lists the incidence and/or prevalence of the disease in the United States and other selected geographic regions, when appropriate. In some instances, when the incidence varies between genders, ethnicity, or race, this information is noted as well. For certain diseases with insufficient data on incidence or prevalence, other terms such as rare, infrequent, or unknown are used. The reader is cautioned to use this information only as a general indicator of disease prevalence. For some diseases, prevalence may vary by geographical area.
- C The indication section refers to the use of apheresis in specific situations encountered in the disease (e.g., antibody-mediated rejection [indication] in the setting of cardiac transplantation[disease]).
- D The type of therapeutic apheresis procedure is listed here. For certain diseases, there are several apheresis-based modalities available. In such instances (e.g., lung transplantation), more than one type of therapeutic apheresis modality is listed.
- E Recommendation grade is assigned to each categorized entity. As noted in the text, the authors used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading the level of clinical recommendation.
- F The ASFA category is listed for each therapeutic apheresis modality discussed.
- G This section lists the number of patients reported in the literature who were treated with therapeutic apheresis. The Committee used three categories: fewer than 100, between 100 and 300, and more than 300. This entry will help readers in judging how often this entity was reported to be treated with therapeutic apheresis. However, the number of patients treated is often less important than the quality of the scientific reports.
- H This section is used when there are several different therapeutic apheresis procedures used, and it was necessary to subdivide available scientific reports, as well as in the situation when different subsets of patients are being analyzed. Not all entries will have this section.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37/100,000/yr (US)		Procedure TPE	Recommendation Grade 1A	Category I
No. of reported patients: > 300	RCT 7(301)	CT 2(133)	CS 38(1541)	CR N/A

Description of the disease

Thrombotic thrombocytopenic purpura (TTP), also known as TMA-ADAMTS13 deficiency, is a systemic thrombotic illness affecting mostly small vessels. Originally defined by the pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), mental status changes, renal failure, and fever, currently, clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4–8 h of diagnostic suspicion, after other causes of systemic TMA such as disseminated intravascular coagulopathy, severe malignant hypertension, pernicious anemia (vitamin B12 deficiency), HUS, and post-transplant TMA have been considered unlikely and working clinical diagnosis of TTP is made. TTP is associated with a severe (<10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of VWF multimers. Severe ADAMTS13 deficiency becomes a corner stone for making a diagnosis of TTP; however, lacking so does not exclude TTP. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Autoantibody presence in the majority of patients with idiopathic acquired TTP and severe ADAMTS13 deficiency suggests an acquired autoimmune disorder. IgG4 is the most common anti-ADAMTS13 IgG subclass and appears to be related to disease recurrence. Pregnancy, connective tissue disease, medications, infection, cancer, and transplantation are associated with TTP, HUS, and TMA syndromes. Diagnostic criteria to differentiate TTP from different types of HUS (characterized by TMA, thrombocytopenia, and renal failure) are still evolving.

Current management/treatment

TPE has decreased overall mortality of idiopathic TTP from nearly uniformly fatal to < 10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Corticosteroids are often used as an adjunct at 1 mg/kg/day; however, no definitive trials proving their efficacy have been performed. Rituximab is now often used to treat refractory or relapsing TTP and recent studies have described incorporation of rituximab as adjunctive agent with initial TPE. Since rituximab immediately binds to CD20-bearing lymphocytes, a 18–24 h interval between its infusion and TPE is used in practice. Other adjuncts include cyclosporine, azathioprine, vincristine, and other immunosuppressive agents. Splenectomy was used in the past. Although platelet counts can be very low, patients with TTP have thrombotic rather than hemorrhagic tendency. Bleeding, if present, is typically limited to skin and mucous membranes. Platelets should only be transfused for significant clinical indications such as potential life-threatening bleeding. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10–15 mL/kg) or cryoprecipitate (which contains ADAMTS13) or plasma derived von Willebrand factor concentrates (used to treat von Willebrand disease) have been used. Most recently the use of anti-von Willebrand antigen antibody is being evaluated.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. One hypothesis is that TPE removes anti-ADAMTS13 autoantibody, while replacing ADAMTS 13 protease activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

Technical notes

Transfusion of RBC, when medically necessary, may be given emergently around the time of apheresis. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio (to whole blood) to minimize citrate reactions, especially for patients with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with cryoprecipitate poor plasma as replacement. One recent study showed that the use of cryoprecipitate poor plasma as replacement may be associated with more frequent acute exacerbations. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma (O'Brien, 2013). Albumin alone without any plasma replacement or infusion however has never shown efficacy.

Volume treated: 1–1.5 TPV
Replacement fluid: Plasma

Frequency: Daily

Duration and discontinuation/number of procedures

TPE is generally performed daily until the platelet count is $>150 \times 10^9/L$, and LDH is near normal for 2–3 consecutive days. Role of tapering TPE over longer duration has not been studied prospectively but is used frequently. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

Comité d’Ethique des Centres d’Investigation Clinique de l’inter-région Rhône-Alpes-Auvergne



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Clermont-Ferrand, le 23/08/2017

Cher Monsieur,

Nous vous prions de prendre connaissance de l'évaluation de votre projet présenté au CECIC en date du 22/08/2017. Cette décision a été rendue après revue de votre projet selon la loi Française sur la Recherche Impliquant la Personne Humaine [1] et la déclaration de Déclaration d'Helsinki de l'Association Médicale Mondiale [2].

Le présent avis n'exempte pas le porteur du présent projet du respect de la législation en vigueur à la date d'émission dudit avis.

[1] Chapitre Ier du titre II du livre Ier de la première partie du Code de la Santé Publique relatif aux recherches impliquant la personne humaine.

[2] Déclaration d'Helsinki de l'Association Médicale Mondiale. Principes éthiques applicables aux recherches médicales sur des sujets humains [<http://www.wma.net/f/policy/b3.htm>].

Date de la réunion	22/08/2017
N° IRB	5891
Membres présents	Abergel A, Dualé C, Dubray C, Lambert C, Mourgues C.
Membres excusés	Pereira B.
Expertise extérieure	NA
Titre du projet soumis	<i>Safety and effectiveness of citrate regional anticoagulation for membrane based therapeutic plasma exchange in intensive care unit.</i>
Porteur du projet	Peigne V.
N° de dossier IRB	2017-10
Service	Réanimation médicale, CH Chambéry
CHU de rattachement	Grenoble
Autres destinataires	CECIC

Le CECIC, à la lecture des documents fournis :

- rapport d'une recherche sur des données existantes issues du soin hospitalier, réalisé chez des patients nécessitant des échanges plasmatiques répétés ;
- référencement de la technique d'anticoagulation par citrate (*cf. Lee & Arepally, J. Clin. Apher. 2012;27: 117*) dans cette indication ;
- utilisation du dispositif médical (MacoPharma ACD formule A) conforme à sa notice d'utilisation ;

et, considérant le caractère courant et usuel d'un suivi régulier chez ces

patients, ne relève pas de problème éthique à la publication de ce travail.

Il est toutefois signalé que, compte-tenu

- qu'il ne s'agit pas d'un essai contrôlé randomisé ;
- que le plan d'étude n'est pas adapté à une étude de tolérance ;
- que la magnésémie n'a pas été vérifiée de façon systématique ;

il n'est pas recommandé de déclarer dans la publication que la technique employée est sûre.

En cas de publication de ce travail, voici une suggestion de formulation pour attester de l'obtention de l'avis favorable du CECIC Clermont-Ferrand :

« Un avis éthique consultatif favorable a été obtenu le 23/08/2017 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891) ».

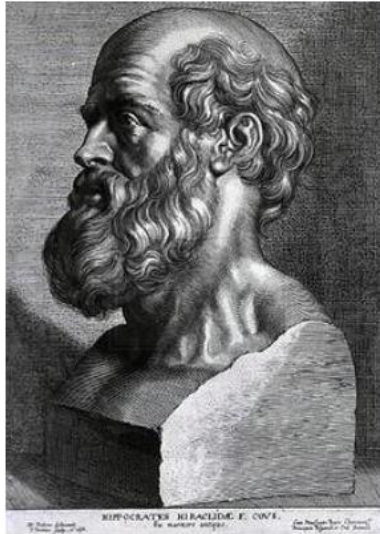
« Study ethics approval was obtained on 23 August 2017 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891) ».

Avec nos sentiments les meilleurs.

Dr Christian DUALÉ, Médecin Délégué
Coordonnateur

Pr Claude DUBRAY, Médecin





SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

