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Regional citrate-calcium anticoagulation during polymyxin-B hemoperfusion: A case series

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Abstract

Introduction: So far, only heparin-based anticoagulation has been proposed during polymyxin-B hemoperfusion. However, postsurgical septic patients can be at high risk of bleeding due to either surgical complications or septic coagulation derangement. Consequently, heparin should not represent in some cases the anticoagulation regimen of choice in this type of patients.

Methods and results: We present a case series of four postsurgical septic patients treated with polymyxin-B hemoperfusion using regional citrate anticoagulation. All the treatments were performed without complications. During each treatment, there were no episodes of filter clotting, no bleeding, and no metabolic complications for any of the patients.

Conclusion: To our knowledge, this is the second published report on the use of citrate anticoagulation during polymyxin-B hemoperfusion. Our case series continued to show that regional citrate anticoagulation regimen is feasible and safe during polymyxin-B hemoperfusion treatment in postsurgical septic patients.

Keywords

Polymixin-B hemoperfusion, citrate anticoagulation, septic shock, septic coagulation derangement

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Introduction

During extracorporeal blood purification treatments, including continuous renal replacement therapy (CRRT) and hemoperfusion treatments, the patient's blood is in contact with the artificial material of the extracorporeal circuit.[1] This phenomenon leads to the activation of platelets (PLTs) and plasmatic coagulation. Consequently, anticoagulation is required during CRRT and hemoperfusion treatments in order to prolong filter survival or to prevent filter clotting. Unfractionated heparin is still widely used as an anticoagulant because of its wide availability, short half-life, and low cost.[2] Furthermore, several centers still use heparin because of the strong experience with the use of this drug, the availability of antagonist (protamine), and the feasibility of monitoring with routine test (activated clotting time (ACT)). However, the use of heparin can have several drawbacks.[2] Heparin anticoagulation is associated with bleeding complications and heparin-induced thrombocytopenia (HIT).[3] These complications represent remarkable challenges, especially in postsurgical septic

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Systemic ionised calcium (mmol/L)	*Adjustment calcium infusion*
<0.90	CaCl2 10 mg/kg bolus + Increase by 10 ml/h
0.90-0.99	Increase by 5 ml/h
1.0-1.3 (Target Range)	No change
1.31-1.40	Reduction by 5 ml/h
>1.40	Reduction by 10 ml/h
Post-filter ionised calcium (mmol/L)	***Adjustment of citrate infusion***
<0.2	Reduction by 10 ml/h
0.2-0.5 (Target Range)	No change
0.51-0.6	Increase by 10 ml/h
>0.6	Increase by 15 ml/h

Figure 1. Citrate-calcium anticoagulation protocol.

patients. Consequently, alternative anticoagulation regimens have been proposed to overcome this issue. Regional citrate anticoagulation is increasingly popular and is now considered the anticoagulation regimen of choice during CRRT. Several studies have reported a longer circuit survival and a lower rate of bleeding complications when citrate was used as anticoagulant.[4–6] Consequently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended using regional citrate anticoagulation rather than heparin during CRRT.[7]

Hemoperfusion therapy with polymyxin-B (PMX-B) immobilized fiber cartridge PMX-B hemoperfusion (PMX-HP) is a blood purification technique that adsorbs and removes circulating lipopolysaccharide through PMX-B, fixed on the cartridge fibers;[8] this PMX-HP is indicated for septic shock caused by Gram-negative infections.[9] Following the manufacturer's instructions, only heparin-based anticoagulation is suggested during PMX-HP. During hemoperfusion blood purification modality, the complex citrate-calcium formed using regional citrate-calcium anticoagulation modality could not be removed and this is the reason why anticoagulation choice in this case still remains heparin based. However, in some cases postsurgical septic patients are at high risk of bleeding and heparin should not represent the anticoagulation regimen of choice in this kind of patients. In addition, the complex citrate-calcium formed in the blood during 2 h of treatment working at a blood flow of 100 mL/min is not relevant.

After having reviewed the literature, citrate anticoagulation during hemoperfusion treatment with PMX-B was used only once, with remarkable results.[10] In our previous study, we reported a clinical case of a postsurgical septic patient with a high risk of bleeding in which we performed two cycles of PMX-B hemoperfusion treatments using citrate-calcium as regional anticoagulation. In light of the safety and good results obtained, we decided to continue using citrate-calcium as the regional anticoagulation of choice during PMX-HP treatments. We present a series of four different cases of PMX-HP treatments using regional citrate as anticoagulation agent in postsurgical septic patients.

Methods and results

We performed PMX-HP through EstorFlow® hemoperfusion system (Medica S.p.A., Medolla, Italy), a hemoperfusion blood module with a dedicated software for performing PMX-HP treatment. This software guides the user through all steps of the procedure in order to arrange the treatment. We set up blood flow at 100 mL/min; each treatment lasted only 2 h. We used the anticoagulant syringe pump mounted on machine with the dedicated software for managing citrate infusion while calcium reinfusion was managed through the use of an external syringe pump.

PMX-HP treatment using regional citrate anticoagulation was set up using an adaptation of the protocol used for continuous veno-venous hemodialysis ((CVVHD) calcium-citrate CVVHD Fresenius System).[11] In fact, in our hospital, we followed a specific protocol for citrate anticoagulation (as shown in Figure 1). In particular, we used a concentrated solution of citrate (trisodium citrate 4%—citrate 136 mmol/L) in the pre-blood pump. This concentration allowed us to obtain the maximum anticoagulation effect while administering a low volume of citrate. The citrate infusion was estimated to begin at a blood citrate concentration of 3.0 mmol/L (according to the formula shown in Figure 2). Citrate infusion was then adapted to maintain a post-filter calcium concentration around 0.35 mmol/L and systemic calcium was infused through a central venous line in order to prevent hypocalcemia. We also monitored the post-filter calcium concentration in order to accurately titrate citrate infusion. Furthermore, a strict monitoring of systemic pH, bicarbonate, base excess (BE) was carried out in order to detect metabolic complications. Clinical parameters and monitoring data from PMX- HP treatments are shown in Tables 1 and 2 (data are expressed as mean and standard deviation).

$$Citrate\ infusion\ rate\ \left(\frac{ml}{h}\right) = \left[\frac{Blood\ flow\ \left(\frac{ml}{\min}\right) \times Citrate\ dose\ for\ anticoagulation\ \left(\frac{mmol}{l}\right)}{Citrate\ concentration\ in\ the\ bag\left(\frac{mmol}{l}\right)}\right] \times 60$$

Figure 2. Formula used to obtain citrate infusion rate.

Table 1. Clinical parameters on admission, pretreatment, after 12, 24, and 48 h, and at discharge.

	Admission	Pretreatment	T_{12h}	T_{24h}	T_{48h}	Discharge
Mean blood pressure (mmHg)	66 (18.2)	66 (18)	87 (8.7)	100 (14.4)	100 (16)	105 (13.6)
Heart rate (bpm)	87.5 (38)	84 (27)	71 (19.7)	77.2 (19.5)	69 (13)	71.7 (5.1)
Temperature (°C)	36.7 (0.7)	36.2 (0.7)	36 (0.2)	36.5 (0.5)	36.6 (0.7)	36.5 (0.4)
Norepinephrine (μg/kg/min)	0.13 (0.15)	0.29 (0.03)	0.2 (0.1)	0.11 (0.15)	0.05 (0.08)	0 (0)
PaO_2/FiO_2	264.2 (133)	146 (45)	200 (90)	208 (107)	239.7 (116)	380 (224)
PEEP	2.5 (5)	6.25 (4.5)	5.7 (4)	5.7 (4.9)	4.57 (5.2)	0 (0)
pH	7.29 (0.12)	7.28 (0.1)	7.37 (0.05)	7.43 (0.07)	7.46 (0.02)	7.43 (0.07)
BE	−12.5 (9.19)	−8.4 (8.5)	−2.85 (5.5)	4.4 (4.3)	5.5 (3.6)	4.8 (3.4)
Lactate (mmol/L)	4.95 (4.3)	6.32 (4.62)	4.1 (3.2)	2.15 (1.12)	2.3 (1.6)	0.8 (0.3)
Urine output (mL/kg/h)	1 (1)	0.45 (0.42)	1.6 (0.9)	1.3 (0.6)	1.3 (0.7)	1.35 (0.17)
Serum creatinine (mg/mL)	1.99 (0.95)	2.04 (0.79)	1.56 (0.43)	1.74 (1)	1.82 (1)	1.22 (1.04)
BUN	35.75 (23.3)	36.5 (21.8)	31.5 (16.4)	46.7(32.5)	60 (35)	44.5 (39)
Procalcitonin (ng/mL)	34.9 (64.5)	54.7 (56.6)	56.42 (57.38)	45 (58)	28.4 (46)	0.84 (0.6)
White blood cells count (cells/mm³)	13,932 (11,039)	13,505 (11,269)	15,927 (13,838)	17,372 (10,121)	12,351 (10,189)	9030 (4054)
Platelets (cells/mm³)	103,750 (68,516)	86,000 (35,374)	98,000 (30,110)	93,750 (41,756)	87,250 (59,421)	185,250 (77,860)
INR	1.44 (0.31)	2.3 (1)	1.53 (0.44)	1.36 (0.25)	1.25 (0.2)	1 (0.02)
aPTT	41 (8.5)	45 (12)	39.7 (11.5)	35.4 (8)	34.9 (10.6)	30 (2.18)
Bilirubin (mg/dL)	0.52 (0.54)	1 (0.3)	1.7 (0.7)	1.6 (0.5)	1.46 (0.7)	0.9 (0.6)
Hb (g/L)	9.5 (0.72)	9.4 (1.4)	9.2 (1)	9.2 (1)	8.6 (0.3)	10 (0.36)
EAA (EU)	NA	0.74 (0.13)	NA	NA	NA	NA
SOFA score	8 (5.9)	12.5 (1)	11.2 (1.25)	9 (2.4)	8.7 (3.3)	2.5 (1.7)

PEEP: positive end expiratory pressure; BE: base excess; BUN: blood urea nitrogen; INR: international normalized ratio; aPTT: activated partial thromboplastin time; Hb: hemoglobin; EAA: endotoxin activity essay; NA: not available; SOFA: sepsis-related organ failure assessment score; bpm: beats/min. Data are expressed as mean (standard deviation).

Table 2. Data from the first and second cycles of polymyxin-B hemoperfusion treatment.

	pH	BE	Serum sodium (mmol/L)	Ionized calcium (mmol/L)	Post-filter calcium (mmol/L)	Citrate infusion rate (mL/h)	Calcium reinfusion rate (mL/h)	Total calcium reinfused (mg)
First cycle of Polymyxin-B hemoperfusion treatment								
T_0 (basal)	7.34 (0.07)	−5.6 (5.9)	137 (1.8)	1.02 (0.08)	–	–	–	–
T_1 (10 min)	7.34 (0.06)	−4.5 (5.1)	137 (1.3)	0.98 (0.1)	0.29 (0.07)	132.4 (10.9)	8.9 (5.7)	–
T_2 (30 min)	7.35 (0.06)	−3.96 (5)	137.8 (2.16)	1.02 (0.13)	0.31 (0.04)	132.4 (10.9)	8.6 (6.1)	–
T_3 (60 min)	7.37 (0.08)	−3.94 (5.3)	137.2 (2.6)	1 (0.13)	0.31 (0.05)	132.4 (10.9)	10.6 (9.4)	–
T_4 (90 min)	7.37 (0.07)	−3.16 (5.6)	137.4 (1.8)	0.96 (0.2)	0.29 (0.06)	134.4 (8.7)	10.4 (9.7)	–
T_5 (120 min)	7.39 (0.08)	−2.24 (5.6)	137.4 (2.19)	1 (0.2)	0.3 (0.04)	134.4 (8.7)	10.4 (9.7)	608 (410)
Second cycle of Polymyxin-B hemoperfusion treatment								
T_0 (basal)	7.43 (0.08)	2.5 (7.3)	136.7 (3.2)	1.15 (0.07)	–	–	–	–
T_1 (10 min)	7.4 (0.06)	2.06 (6.7)	137 (2.64)	1.15 (0.03)	0.32 (0.02)	137.7 (11.5)	5.3 (6.8)	–
T_2 (30 min)	7.41 (0.06)	3.13 (7.2)	136.6 (3.2)	1.11 (0.08)	0.32 (0.02)	139 (9.6)	4.7 (7.23)	–
T_3 (60 min)	7.42 (0.07)	3.73 (7)	136.7 (2.5)	1.07 (0.09)	0.32 (0.02)	139 (9.64)	7 (8.5)	–
T_4 (90 min)	7.38 (0.07)	−3.16 (5.6)	137.4 (1.8)	0.96 (0.2)	0.29 (0.06)	134.4 (8.76)	9.6 (7.5)	–
T_5 (120 min)	7.39 (0.08)	−2.24 (5.6)	137.4 (2.2)	1 (0.2)	0.3 (0.04)	134.4 (8.76)	0.6 (7.5)	820 (620)

BE: base excess.
Data are expressed as mean (standard deviation).

Case description

Case 1

A 78-year-old man was admitted to our intensive care unit (ICU) for septic shock due to anastomotic leakage after a right hemicolectomy. He arrived from the operating room where he underwent a leakage repair and ileostomy procedure. He was sedated and intubated and mechanical ventilation was continued with low tidal volume (6 mL/kg). Hemogas-analysis showed metabolic acidosis (pH 7.3; lactate 4 mmol/L) and central venous saturation was 65%. After fluid resuscitation, we started norepinephrine infusion with increasing adjustment of the dose (up to 0.25 μg/kg/min). Blood cultures, bronchoalveolar lavage, and surveillance swabs were collected. This was followed by administration of broad-spectrum antibiotics (piperacillin/tazobactan, tygecyclin and fluconazole 800 mg/day) and we also administered intravenous immunoglobulin therapy (IgM-enriched preparation, dose 5 mL/kg/day, for three consecutive days). Endotoxin activity (Endotoxin Activity Assay, Spectral Medical Inc., Toronto, Canada) on admission was registered (EA=0.75). In light of the clinical and laboratory findings, we began PMX-HP using citrate regional anticoagulation because of the increased risk of bleeding in this patient (recent surgery, low PLT count 41,000/mm^3) and altered coagulation parameters (international normalized ratio (INR): 2.6; activated partial thromboplastin time (aPTT): 47 s). Due to the rapid clinical improvement, we decided to perform only the first treatment with PMX-HP. During the cycle, there were no episodes of filter clotting, no bleeding, and no metabolic complications (i.e. hypocalcemia/hypercalcemia or metabolic disorders). The total volume of citrate infused during the cycle was 260 mL (35.4 mmol). Clinical conditions rapidly improved in the following days, enabling weaning from mechanical ventilation. The patient was discharged from the ICU on the 10th day after admission, in good general condition.

Case 2

A 59-year-old man was admitted to the ICU for postoperative monitoring following neurosurgical removal of recurrent craniopharyngioma. The patient had already undergone three surgical interventions and several radio-chemotherapy cycles. He also presented the following comorbidities: chronic obstructive pulmonary disease (COPD), type 2 diabetes, and arterial hypertension. Furthermore, he presented a recent history of severe acute exacerbated COPD (2 months prior to surgery).

The postoperative course was complicated by the onset of hydrocephalus, surgical wound infection, and ventriculitis and the patient became colonized with *Klebsiella pneumoniae* Carbapenemase Producer (KPC). On the 20th day after admission, the patient developed septic shock due to Gram-negative bacteria. Endotoxin activity was 0.9 and a KPC presence was detected in blood cultures (collected during the febrile peak). Consequently, septic shock therapies were started: antibiotic therapy, vasoactive support (norepinephrine 0.35 μg/kg/min, vasopressin 0.2 U/min), and intravenous immunoglobulin therapy (pentaglobin 250 mg/kg/day). Furthermore, we performed coupled plasma filtration and adsorption treatment (CPFA) using citrate as regional anticoagulant. Despite maximal therapy, we did not observe clinical improvements but a progressive, serious, and continuous worsening of the clinical picture. Due to high endotoxin activity, an altered coagulation pattern (PLTs: 67,000; INR: 2.9; aPTT: 56), and recent intracranial surgery we decided to initiate a hemoperfusion cycle with PMX-HP using regional citrate anticoagulation. Two cycles were performed successfully and without complications. The total volume of citrate infused during the first and second cycles was 248 and 268 mL respectively (70.1 mmol in total). In the following days the clinical picture improved and therefore the vasoactive and respiratory supports were progressively reduced. Due to the persistence of the hydrocephalus, the patient underwent ventricular-peritoneal shunt placement. After 2 months of hospitalization, the patient was discharged from the ICU with good clinical signs.

Case 3

A 76-year-old man was admitted to intensive care after a radical cystectomy with orthotropic neo-bladder complicated by significant intraoperative bleeding, requiring transfusion of five units of blood and of 1500 mL of fresh frozen plasma. He also presented the following comorbidities: arterial hypertension and previous nephrectomy. At the moment of admission, he was sedated, intubated, and mechanically ventilated. Hemodynamics was not supported by vasoactive drugs. Due to the occurrence of atrial fibrillation, electrical cardioversion was promptly attempted and sinus rhythm was restored. The patient was extubated the following day.

On the fourth day after admission, we observed a worsening of the clinical scenario characterized by fever, abdominal pain during physical examination, and increase of inflammatory indices (i.e. procalcitonin (PCT) and white blood cells count). The abdominal computed tomography (CT) scan revealed a dehiscence of the ileo-ileal anastomosis. Consequently, the patient was immediately taken to the operating room for anastomosis repair. After surgery, clinical conditions were critical: hemodynamic instability requiring vasoactive support (norepinephrine 0.35 μg/kg/min), contraction of diuresis (0.3 mL/kg/h), and worsening of the respiratory exchanges (PaO_2/FiO_2 ratio of 200). Despite specific sepsis therapies, general conditions were severe. Taking into account the endotoxin activity level (EA=0.79), we decided to start the hemoperfusion treatment

with PMX-HP, choosing calcium citrate as regional anticoagulation due to the low PLT count (37,000/mm^3) and the bleeding tendency observed during surgical interventions. The two cycles were completed without complications. The total volume of citrate infused during the cycle was 246 mL for each treatment (71.8 mmol in total). Gas exchange and hemodynamic parameters gradually improved, the patient was weaned from mechanical ventilation, and was extubated 3 days later. After 20 days of hospitalization, the patient was discharged from the ICU in good clinical condition.

Case 4

A 76-year-old woman entered the emergency department with high fever, shiver, low back pain, and disorientation. Comorbidities included: peripheral vascular disease, paroxysmal atrial fibrillation, and cerebral ischemia without neurological sequels. Her medical status progressively deteriorated and, therefore, she was admitted to our ICU for septic shock due to urinary tract infection. At admission, the patient was breathing spontaneously with acceptable respiratory exchange, no signs of respiratory fatigue, but with significant cardiovascular and metabolic effort. She was severely hypotensive (mean arterial pressure (MAP) 40 mmHg), tachycardia atrial fibrillation (120 beats/min (bpm)), oligo-anuric, and with lactic acidosis (pH 7.16, BE −19.1 mmol/L, lactate 10.9 mmol/L). PCT was high (PCT > 100 ng/mL) as well as white blood cells count. Norepinephrine infusion was started (up to 0.28 µg/kg/min) as well as broad-spectrum empirical antibiotic therapy. Echocardiographic examination showed a ventricular systolic dysfunction and levosimendan infusion (0.1 µg/kg/min) was started. Despite vasopressor and inotropic support, the clinical conditions did not improve. High level of endotoxin activity (EA) was registered (EA = 0.84), consequently, it was decided to initiate hemoperfusion therapy with PMX-HP. In light of the patient's prohemorrhagic profile (INR: 1.79; PLT: 48,000), confirmed also during thromboelastography (TEG®) analysis (R16.4, K 3.8, α 44.7, maximum age (MA) 61.9, confidence interval (CI)-9), it was decided to use calcium citrate as a regional anticoagulant system. The treatment lasted 2 h. We repeated a second treatment 12 h later. The two cycles were completed without complications. The total volume of citrate infused during the cycle was 300 mL for each treatment (81.6 mmol in total). After the second cycle, we observed a progressive recovery of clinical condition with improvement of cardiovascular and metabolic parameters (MAP 100 mmHg, heart rate 93 bpm sinus rhythm, pH 7.34, BE–6.4 mmol/L, and lactates 3.6 mmol/L). Vasoactive support was progressively reduced. The patient was transferred to the medical ward in good general condition after 9 days of hospitalization in ICU.

Discussion

This case series described four clinical cases about the possible use of citrate as a regional anticoagulation during PMX-HP in postsurgical septic patients. The seven cycles of PMX-HP were performed without complications (i.e. no filter clotting, no metabolic complications, and no sodium load).

PMX-HP therapy is an effective method for removing endotoxin in the bloodstream and it is a well-established therapy for septic shock caused by endotoxemia in patients who are unresponsive to conventional treatment.[12] After publication of the Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) trial,[9] in further some recent trials, the use of PMX-HP in septic shock after abdominal surgery failed to show any improvement in outcome in comparison with the conventional treatments.[13,14] However, these trials suffered from some important methodological limitations, as reported in an editorial by Antonelli and Ronco.[15] Furthermore, PMX-HP presented interesting effects in septic shock patients, especially on hemodynamic, oxygenation, and mortality in several trials.[9,16,17] Consequently, while still awaiting the results of Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES) and the EUPHAS-2 trials to obtain more accurate results, so far, we continue to perform PMX-HP treatments in patients with endotoxic septic shock unresponsive to conventional therapy. Anyway, the main goal of this cases series is focused on showing the feasibility of regional citrate-calcium anticoagulation modality during of PMX-HP, and not therapy effectiveness.

Currently, heparin anticoagulation represents the regional anticoagulation regimen of choice during PMX-HP. However, postsurgical septic patients are at high risk of bleeding, sometimes life-threatening, due to either surgical complications or to septic coagulation derangement (i.e. dysfunctional anticoagulation pathways, dysfunctional fibrinolysis, or thrombocytopenia).[18–20] Not to be underestimated, the use of heparin is associated with a higher risk of bleeding and heparin-induced thrombocytopenia (HIT).[3] At the same time, during an extracorporeal treatment, the risk of cartridge clotting is extremely high without an optimal coagulation regimen. During CRRT, regional anticoagulation with citrate has shown to be superior to heparin anticoagulation with regard to safety and to prolong circuit survival and citrate now represents the first choice of anticoagulation for CRRT.[21] Consequently, in light of these evidences and of the interesting result obtained in our previous case report, we decided to perform PMX-HP treatment with citrate.[10] The major worries of using citrate anticoagulation are metabolic complications (i.e. acidosis and alkalosis), calcium control (to prevent both hypocalcemia and

hypercalcemia), and sodium load.[22] However, when a well-designed protocol is strictly followed, citrate provides good metabolic control. In fact, we respected a precise protocol for citrate anticoagulation, as described above. For each patient, during the two cycles, there were no episodes of filter clotting, no bleeding, and no metabolic complications.

Conclusion

Our case series show that regional citrate anticoagulation regimen is feasible and safe during PMX-HP treatment in postsurgical endotoxic septic shock patients. We strongly believe that regional citrate anticoagulation should be considered as an anticoagulation modality during PMX-HP treatment, especially in patients at high risk of bleeding.

Declaration of conflicting interests

C. R. received an Honoraria from Toray, Asahi, Estor, GR, and Baxter. The other authors report no conflict of interest.

Ethical approval and consent to participate

Following the rules of our local ethics committee, written informed consent to participate and to publish this case report was obtained from the patients.

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