Case Report

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Coupled Plasma Filtration Adsorption in Patients with a History of Kidney Transplantation: Report of Two Cases

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Rhabdomyolysis · Sepsis · Myoglobin · Cytokines · Graft survival

Abstract
Coupled plasma filtration adsorption (CPFA) is an extracorporeal treatment based on plasma filtration associated with an adsorbent cartridge and hemofiltration. CPFA is able to remove inflammatory mediators and it has been used to treat severe sepsis, septic shock and multiple organ dysfunction syndrome. Limited experience exists on the use of CPFA after solid organ transplantation. We report our experience with CPFA in 2 kidney transplant recipients with post-nephrolithotomy septic shock and severe unexplained rhabdomyolysis. In both the cases, excellent results were observed. In selected cases, CPFA can be safely and effectively used in patients with a solid organ transplant. However, additional studies are needed in this particular setting, to further investigate the potential role of CPFA for the treatment of other conditions associated with excessive inflammation, such as in rheumatologic disorders and delayed graft function.

Introduction

Coupled plasma filtration adsorption (CPFA; Bellco S.r.l., Mirandola, Mo., Italy) is an extracorporeal treatment combining plasma filtration with an adsorbent cartridge and hemofiltration [1]. The main clinical application of CPFA is the treatment of sepsis [2–5]. The hydrophobic resins in the cartridge can absorb a wide range of pro-/anti-inflammatory mediators thus allowing the removal of the inflammatory mediators responsible for the development and maintenance of septic shock and multiple organ dysfunction syndrome. Other treatment modalities previously used to treat sepsis (drugs, monoclonal antibodies, other extracorporeal treatments) are mainly directed against a single substance or mediator. This high selective effect seems to represent their major limitation [6].

CPFA is likely to be a therapeutic option for severe rhabdomyolysis. In fact, the resin contained in the CPFA cartridge presents a highly adsorbing surface due to the great number of suitable pores that are capable of capturing molecules. The maximum of efficacy is obtained especially in case of substances with high-medium molecular weight, like myoglobin (about 18 kDa). On the other

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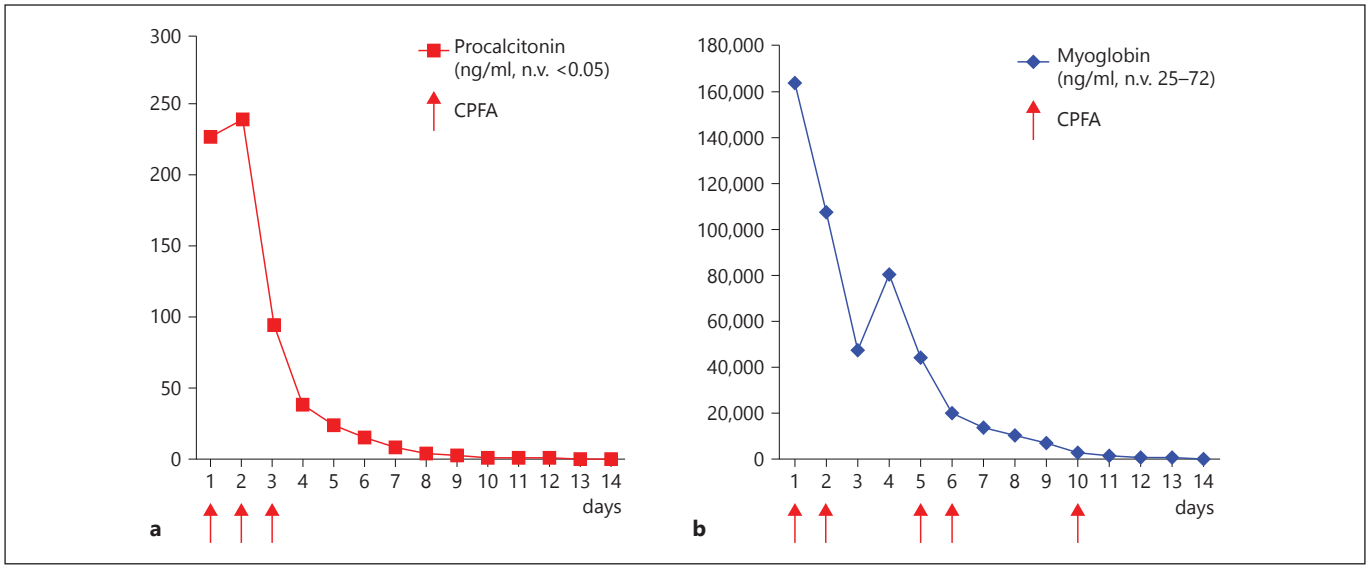

Fig. 1. a CPFA effect on serum procalcitonin levels in patient 1. **b** CPFA effect on serum myoglobin levels in patient 2.

hand, this molecule is typically not well removed by conventional dialysis filters [7].

Limited data exist on the use of CPFA in the setting of solid organ transplantation [8]. We herein report our experience with 2 patients who had a history of kidney transplantation.

Case Report

Case 1

A 64-year-old Caucasian man suffering from autosomal dominant polycystic kidney disease received his first deceased donor kidney transplant in May 2014. He was given extended-release tacrolimus, mycophenolate mofetil and steroids for immunosuppression. Past medical history included hypertension, T cell-mediated acute rejection and new-onset diabetes after transplantation. Three months after transplantation, the patient developed graft hydronephrosis due to an obstructing calculus in the renal pelvis. The stone was initially treated with extracorporeal shock wave lithotripsy and percutaneous nephrostomy placement. However, no significant improvement was observed. One month later, the patient was further hospitalized with a plan for surgical removal of the residual debris. At the time of surgery, serum creatinine (sCr) was 2.52 mg/dl, and systemic inflammation parameters were normal. Few hours after the procedure (percutaneous nephrolithotomy), the patient became pyrexial and hemodynamically unstable (blood pressure 70/40 mm Hg). Dopamine infusion of 15 μg/kg/min was started, with minimal improvement. Blood tests showed worsening graft function (sCr 4.81 mg/dl) and significantly increased procalcitonin levels (228 ng/ml). The patient was immediately transferred to the intensive care unit with a diagnosis of septic shock. Immunosuppression was stopped except for intravenous (IV) administration of 20 mg methylprednisolone daily. Antibiotic therapy with 500 mg IV meropenem administered 3 times a day and oral ciprofloxacin of 500 mg daily was started. Three consecutive sessions of CPFA were also performed: continuous hemofiltration was given for 8 h during each treatment. Following treatment with CPFA, the patient's clinical condition rapidly improved with sustained normalization of blood pressure and procalcitonin (fig. 1a). After 4 days, the patient was stepped down but his graft function never recovered. To minimize the risk of recurrent infection and safely stop immunosuppression, we then decided to perform a graftectomy. The surgical procedure and the post-operative course were uneventful, and the patient was eventually discharged 8 days later. The clinical course is summarized in table 1.

Case 2

A 65-year-old Caucasian woman suffering from autosomal dominant polycystic kidney disease received a deceased donor renal transplant in 1998. Past clinical history included dyslipidemia, cardiac hypertrophy, secondary hyperparathyroidism and nonvalvular atrial fibrillation. After 15 years of follow-up, she was still on a triple-agent immunosuppressive regimen (cyclosporine, mycophenolate mofetil and steroids), and her graft function was optimal (sCr nadir: 0.9 mg/dl). During March 2014, the patient started complaining of malaise, severe asthenia, diffuse arthralgia and myalgia. Two weeks later, the patient was hospitalized with deteriorating general health condition. On admission, laboratory tests showed an acute kidney failure and severe rhabdomyolysis (zenith of serum myoglobin: 163,630 ng/ml) requiring hemodialysis (zenith sCr: 18 mg/dl). Viral myositis was suspected, but not confirmed in the muscle biopsy. Standard hemodialysis did not manage to effectively remove circulating myoglobin; so we decided to treat the patient with 5 sessions of CPFA, in combination with IV administration of methylprednisolone (50 mg/day). Rhabdomyolysis rapidly resolved with prompt recovery of the renal function (sCr at discharge: 0.9 mg/dl) and normalization of the inflammatory markers (fig. 1b). The clinical course is summarized in table 2.

Table 1. Modification of clinical and blood test data before and after CPFA treatments in patient 1

	Normal values	Baseline value	Adverse event	Before 1st CPFA	Before 2nd CPFA	Before 3rd CPFA	Discharge from ICU
Day from KT, n	–	–	129	130	131	132	134
sCr, mg/dl	0.6–1.2	2.70±0.4*	4.80	6.57	3.81	2.66	3.06
CRP, mg/l	<0.5	0.01±0.007*	10.1	12.7	6.3	4.2	1.5
Procalcitonin, ng/ml	<0.05	0.01±0.002*	228.4	240.8	95.0	38.4	24.5
Lactates, mg/dl	9–16	–	40.5	23.1	22.0	17.8	15.2
WBC, $\times 10^3$	4.8–10.8	3.97±0.82**	4.31	7.28	5.55	7.11	5.67
NLR	–	9.7±1.2**	21.0	29.9	34.2	17.7	12.5
Blood pressure, mm Hg	–	150/89**	70/40	90/60	125/70	120/70	120/60
CI, l/min/m^2	–	–	2.96	3.24	–	3.94	–
SVRI, dynes*s/cm^5*m^2	–	–	666	1,249	–	1,475	–
VIS	–	–	12	6	6	0	0
Temperature, °C	–	36.1±0.5**	39.5	37.8	36.5	36.7	36.0
Diuresis, ml/24 h	–	3,200±270**	300	350	1,300	1,700	2,000

Specific data regarding CPFA procedures	1st CPFA	2nd CPFA	3rd CPFA
Qb, ml/min	150	160	140
Total plasma, ml	8,100	7,200	7,400
Plasma filtration flow rate, %	15	15	15
Total dose of heparin, IU	1,250	1,250	1,250
Qinf, ml/min	25	25	25
Ponderal weight loss, ml/kg	25	0	25

* Nadir and ** median value (from KT to adverse event).

KT = Kidney transplantation; ICU = intensive care unit; CRP = C-reactive protein; WBC = white blood cells; NLR = neutrophil-to-lymphocyte ratio; CI = cardiac index; SVRI = systemic vascular resistance index; VIS = vasoactive-inotropic score; Qb = blood flow; Qinf = blood reinfusion.

Discussion

CPFA has been seldom used in cases of solid organ transplantation recipients. To the best of our knowledge, there is only one study describing CPFA administration for the treatment of hyperbilirubinemia after liver transplantation [8]. No case reports in the setting of kidney transplantation are currently available.

CPFA has been extensively used to treat septic shock [2–5]. However, there is still no consensus, and the best strategy to stop the so-called 'septic cascade' has not been defined. The main benefit of using CPFA is in its ability to remove a wide spectrum of molecules, thus positively modulating the inflammatory systemic framework, in order to clear any imbalance between different types of sepsis mediators. In our experience, CPFA allowed quick clinical recovery in the patient and prompt reversal of the inflammatory imbalance. It is difficult to say if the reduction of procalcitonin values observed in the present case was correlated to its direct removal by CPFA or if it was caused by the clinical improvement of the patient. However, despite more than 20% of this molecule (approximately weighting 13 kDa) being commonly removed by adsorption techniques, we can suppose that its fast normalization is mainly connected with the resolution of the underlying inflammatory process [9].

No experience exists on the use of CPFA to treat severe hypermyoglobinemia. This is the first report of an episode of rhabdomyolysis that was successfully treated with CPFA. Main advantages of using CPFA as compared to standard hemodialysis filters are the following: (a) the ability to effectively remove myoglobin and (b) the chance to simultaneously manage acute kidney failure through continuous veno-venous hemofiltration. In the present case, complete resolution of both rhabdomyolysis and acute kidney injury were observed.

Several complex clinical conditions (i.e. septic shock or rhabdomyolysis) may be effectively treated using CPFA, especially in case of concomitant acute kidney failure. Despite the 2 cases herein reported, we cannot

Table 2. Modification of clinical and blood test data before and after CPFA treatments in patient 2

	Normal values	Baseline value	Adverse event	Before 1st CPFA	Before 2nd CPFA	Before 3rd CPFA	Before 4th CPFA	Before 5th CPFA	At discharge
Day from KT	–	–	5,597	5,604	5,605	5,608	5,609	5,614	5,622
sCr, mg/dl	0.6–1.2	0.90±0.3*	18.00	5.55	3.11	4.63	4.00	3.24	1.08
sGOT, IU/l	0–40	12±2*	488	612	560	221	152	41	20
sGPT, IU/l	0–35	9±3*	164	286	334	296	249	158	50
Uric acid, mg/dl	3.5–7.0	3.0±0.4*	2.0	–	–	6.8	6.4	3.5	3.3
Myoglobin, ng/ml	25–72	–	42,538	163,630	107,356	44,286	20,076	1,495	125
CPK, IU/l	8–150	–	21,201	39,145	20,560	8,826	4,932	589	96
LDH, IU/l	56–194	–	1,824	2,742	2,797	1,668	–	1,090	781
CRP, mg/l	<0.5	0.09±0.01*	5.25	7.99	4.99	1.61	1.25	0.33	0.11
Procalcitonin, ng/ml	<0.05	–	1.38	1.74	0.99	–		0.18	–
WBC, $\times 10^3$	4.8–10.8	5.50±0.12**	13.51	13.70	20.98	9.87	11.29	10.90	9.34
NLR	–	5.4±0.7**	26.2	32.4	21.7	16.3	12.1	7.4	3.5
Blood pressure, mm Hg	–	160/80**	150/80	132/88	180/80	170/85	189/63	170/60	170/65
Temperature, °C	–	36.2±0.5**	37.4	36.5	36.0	36.0	35.7	36.0	36.0
Diuresis, ml/24 h	–	2,750±320**	1,000	100	150	700	800	3,000	2,900

Specific data regarding CPFA procedures	1st CPFA	2nd CPFA	3rd CPFA	4th CPFA	5th CPFA
Qb, ml/min	130	110	150	140	130
Total plasma, ml	6,500	3,300	7,400	8,000	5,400
Plasma filtration flow rate, %	15	13	15	15	13
Total dose of heparin, IU	1,250	1,250	1,250	1,250	1,250
Qinf, ml/min	25	25	32	32	25
Ponderal weight loss, ml/kg	0	0	50	50	50

* Nadir and ** median value (from KT to adverse event).

KT = Kidney transplantation; sGOT = serum glutamate-oxaloacetate transaminase; sGPT = serum glutamate-pyruvate transaminase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; CRP = C-reactive protein; WBC = white blood cells; NLR = neutrophil-to-lymphocyte ratio; Qb = blood flow; Qinf = blood reinfusion.

provide strong evidences, but our experience suggests that CPFA can be safely offered to kidney transplant recipients when indicated. Pro-inflammatory substances like cytokines are commonly involved in several specific pathological processes observed in the transplant setting, such as delayed graft function, recurrence of primary renal disease and uremic hemolytic syndrome. Further studies are required in order to clarify the possible applications of CPFA in this scenario.

Authorship

Q.L. and F.P. designed the research; Q.L., V.D.P. and S.A. wrote the paper; Q.L., V.D.P., S.I., S.A. and K.C. collected the data; L.D.L., A.F. and F.P. participated in the critical evaluation of the paper.

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Conflict of Interest

S.A. is an employee of Bellco S.r.l.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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