Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Coupled-plasma filtration and adsorption for severe burn patients with septic shock and acute kidney injury treated with renal replacement therapy

Filippo Mariano [a,d,*], *Zsuzsanna Hollo'* [a], *Nadia Depetris* [b], *Valeria Malvasio* [c], *Alberto Mella* [a], *Daniela Bergamo* [a], *Anna Pensa* [c], *Maurizio Berardino* [b], *Maurizio Stella* [c], *Luigi Biancone* [a,d]

[a] *Nephrology, Dialysis and Transplantation U, Department of General and Specialized Medicine, City of Health and Science, CTO Hospital, Turin, Italy*

[b] *Anesthesia and Intensive Care 3, Department of Anesthesia and Intensive Care, City of Health and Science, CTO Hospital, Turin, Italy*

[c] *Plastic Surgery and Burn Center, Department of General and Specialized Surgery, City of Health and Science, CTO Hospital, Turin, Italy*

[d] *Department of Medical Sciences, University of Turin, Turin, Italy*

ARTICLE INFO

Keywords:

Coupled-plasma filtration adsorption
Burns
Septic shock
Acute kidney injury

ABSTRACT

Background: Coupled-plasma filtration adsorption (CPFA) is a sorbent-based technology aimed at removing soluble mediators of septic shock. We present our experience on the use of CPFA in septic shock severe burn patients with acute kidney injury (AKI) needing renal replacement therapy (RRT) with the main goal to evaluate efficacy and safety of CPFA in this specific subset of septic shock patients.

Methods: In this observational study, we retrospectively reviewed the medical notes of all burn patients admitted to our adult Burn Center who received CPFA, as part of the septic shock treatment requiring RRT, between January 2001 and December 2017 (CPFA group). We compared CPFA group with all the burn patients admitted to our Center in the same period of time, with the same range of relevant clinical characteristics, who developed AKI and were treated with RRT, but not CPFA (control group). We collected demographic characteristics, burn size, Sequential Organ Assessment Failure (SOFA) score, microbiological data, and patient outcome, in terms of in-hospital mortality rate and the probability of survival calculated using the revised Baux score. We also collected data regarding CPFA safety (hemorrhagic episodes, catheter associated-complications, hypersensitivity reactions) and efficiency (number and duration of CPFA sessions, plasma treated amount, plasma processed dose).

Results: 39 severe burn patients were treated with CPFA (CPFA group) (mean age 46.0 years, range 40.0–56.0 years; mean burn size 48.0% TBSA, range 35.0–60.0% TBSA), and 87 patients

Abbreviations: CPFA, Coupled plasma filtration and adsorption; AKI, Acute kidney injury; CRRT, Continuous renal replacement therapy; MAP, Mean arterial pressure; TBSA, Total body surface area; MRSA, Methicillin resistant staphylococcus aureus; RRT, Renal replacement therapy; RCA, Regional citrate anticoagulation.

* *Corresponding author at*: Nephrology, Dialysis and Transplantation U, Department of Medical Sciences, University of Turin, AOU City of Health and Science, CTO Hospital, Via G. Zuretti 29, 10126 Turin, Italy.

E-mail address: filippo.mariano@unito.it (F. Mariano).

https://doi.org/10.1016/j.burns.2019.05.017

treated with RRT, but not CPFA, who had similar clinical characteristics (control group). Observed mortality rate was 51.3% in the CPFA group and 77.1% in the control group (p 0.004). Regarding factors affecting survival in the CPFA group, SOFA score on the 1st day of CPFA resulted significant (OR 2.016, 95% CI, 1.221–3.326; $p < 0.004$) in the multivariate analysis logistic model.

Conclusions: CPFA treatment for burn patients with AKI-RRT and septic shock, sustained by bacterial strains non or poorly responsive to therapy, was associated with a lower mortality rate, compared to RRT alone. However, further research, such as large prospective studies, is required to clarify the role of CPFA in the treatment of burns with septic shock and AKI-RRT.

1. Introduction

Coupled-plasma filtration adsorption (CPFA) is a sorbent-based technology with an extra-corporeal circuit consisting of a plasma filter, a resin cartridge and a high-flux dialyzer [1]. CPFA is aimed at removing soluble endogenous inflammatory mediators circulating in septic shocks and acute kidney injuries (AKI) via an extracorporeal treatment [1,2]. CPFA pilot applications in human septic shock demonstrated favorable effects, by improving hemodynamic status, reducing norepinephrine requirement, and showing immunomodulation properties [3–5].

In burn patients, AKI requiring renal replacement therapy (AKI-RRT) during septic shocks represents one of the most prejudicial complications, still burdened by a high mortality rate [6–16]. CPFA has been described as a promising emerging purification technique in burns, although there is no large study reporting its application in burn patients so far [14].

After a preliminary experience of good hemodynamic tolerance and metabolic management in burns patients [17,18], starting in January 2001, we used CPFA as an adjunctive modality for severe burn patients with septic shock, AKI-RRT and no clinical response to an appropriate antibiotic therapy.

In this study we present our experience on the use of CPFA in 39 severe burn patients with septic shock and AKI needing RRT with the main goal to evaluate efficacy and safety of CPFA in this specific subset of septic shock patients. Furthermore, we present and examine aspects of the adopted CPFA technique.

2. Material and methods

2.1. Study design

In this observational study, we retrospectively reviewed the medical notes of all burn patients admitted to our adult Burn Center who received CPFA, as part of the septic shock treatment requiring RRT, between January 2001 and December 2017 (CPFA group).

In order to better evaluate efficacy and safety of CPFA, we compared CPFA group with all the burn patients admitted to our Center in the same period, with the same range of relevant clinical characteristics, who developed AKI and were treated with RRT, but not CPFA (control group).

We collected demographic characteristics, burn size in terms of % of total body surface area (TBSA) burned, Sequential Organ Assessment Failure (SOFA) score, frequency of mechanical ventilation treatment, microbiological data, and patient outcome, in terms of in-hospital mortality rate. Regarding SOFA score, brain injury was excluded for all patients in the CPFA group at Burn Center admission, and all of them were sedated the day that CPFA started. As suspension of sedation was not possible for safety reasons, the SOFA score of the central nervous system was conventionally considered +1.

The probability of survival was calculated in each patient using the revised Baux score [19].

We also collected data regarding CPFA safety (hemorrhagic episodes, catheter associated-complications, hypersensitivity reactions) and efficiency (number and duration of CPFA sessions, and plasma processed dose).

The study was conducted according to the Helsinki Declaration and approved by the Ethics Committee of our Hospital (dossier n. CS2/908). Informed consent to the proposed treatments and the consent to retrospectively review the medical notes and analyze the collected data was obtained from the patients or substitute decision-makers.

2.2. Management of septic shock and AKI

Systemic treatment of burn patients and diagnosis and treatment of septic shock was managed by a multidisciplinary team on the basis of guidelines in place at that time [20–28].

RRT was started when patients were in a trend of fluid overload not responsive to conservative management including maximal diuretic therapy and: (1) oliguria or (2) severe hyperkalemia, or (3) severe acidosis or (4) uremic complications [20].

CPFA was chosen as an additional therapy when: (1) the patients were in septic shock with AKI-RRT and multiorgan failure, and: (2) microbiological confirmation of the septic event by means of blood cultures was positive for multidrug-resistant strains, and: (3) there was no clinical response after 72 h of appropriate antibiotic treatment.

2.3. CPFA technique

CPFA was performed with a dedicated machine that the manufacturer updated over time (Multimat B.IC/Lynda/Amplya, Bellco spa, Mirandola, Italy). CPFA was always carried out by using a polyethersulfone plasma filter (0.5 m^2, MPS 05, Bellco) placed in series with a highly permeable

polyethersulfone hemodialyzer (1.4 m^2, BLS814 G, Bellco). Plasmafiltrate was adsorbed on an unselective hydrophobic resin cartridge (140 ml for 70 g, with a surface of about 700 m^2/g) [1,17,18].

According to CPFA protocol, blood flow rate ranging from 100 to 180 ml/min and effluent rates were set by the target of dialysis adequacy. Following the manufacturer instructions over time the effluent resulted from hemodialysis, hemodiafiltration, or hemofiltration modalities [1,5,17,18]. We set an exchange of 3–4 l/hour of effluent at the start to achieve an amount of 30–42 l/day, accomplishing the dialysis target of 20–25 ml/kg/die [20]. This target was irrespective of the patient's residual renal function and dialysate/infusion proportion. Moreover, as these rates were occasionally limited by the efficiency and patency of the vascular access, a dedicated nurse recorded the effective flow rates. According to the manufacturer's protocol, plasma filtration rate was maintained between 15–25% of blood flow rate.

The vascular access of CPFA was provided by 12 F double lumen venous catheter inserted in the jugular or femoral vein.

2.4. Anticoagulation strategies

In order to provide CPFA effectively and safely, either unfractionated heparin or citrate were used for anticoagulation of the extracorporeal circuit, on the basis of the patient-s'characteristics, with the support of our previous experiences [13,17,18]. Specifically, the regional citrate anticoagulation (RCA) strategy was preferred if the patient presented (1) a high bleeding risk (defined as bleeding alert in insertion site catheter, or at tracheostomy, or gastrointestinal tract or in surgical wounds) or (2) frank bleeding necessitating transfusion of packed red blood cells [13,17,18]. If none of these conditions existed, anticoagulation was performed with unfractionated heparin.

If RCA was applied, an ACD-A dispersed solution was infused in predilution mode prepared by nurses immediately before CPFA sessions, or with a specific bag (Citrate, Hospital Service, Scarmagno, Italy: composition (in mmol/l) Na^+148; K^+1.5; Mg^{++} 0.75; Cl^- 108; citrate 10; glucose 5.5; bicarbonate 10) [13,17,18]. Subsequently, after 2012 citrate anticoagulation was carried out through a citrate-containing bag following the manufacturer's instructions (Prismocitrate 18/0, Baxter Italia, Rome, Italy: composition (in mmol/l) Citrate 18; Na^+ 140; Cl^- 86). A standard sterile bicarbonate-containing solution was used with calcium as an infusion (Prismasol 32, Hospal, Mirandola, MO, Italy) or without calcium as dialysate (Ci–Ca, Fresenius Medical Care, Bad Homburg, Germany).

In all patients, a commercial 10% calcium chloride solution was infused by the monitor heparin pump in a separate line at the end of the venous circuit [17,18].

If anticoagulation was achieved with unfractionated heparin, the latter was administered pre-filter and standardized to an initial bolus of 1250 U followed by 1000 U/h. Subsequent adjustments were made accordingly to obtain coagulation parameters of PTT > 60 s. A standard sterile bicarbonate-containing solution was used in the form of a dialysate/infusion (Prismasol 32, Hospal, Mirandola, MO, Italy; composition (mmol/l) Na^+ 140; K^+ 2.0; Ca^{++} 2; Mg^{++} 0.75 Cl^-: 108; bicarbonate 32; acetate 4; glucose 5.5).

2.5. Statistical Analysis

Continuous data are expressed as median with quartiles (the 25th and 75th percentiles), and categorical data as frequencies and percentages. Student T-test, Fisher's exact test or ANOVA with multicomparison Newman–Keuls test were used when appropriate. Multivariate analysis was performed using logistic regression for the total number of nonsurvivor patients to determine the effect on the in-hospital mortality rate of the following variables of interest: age, and SOFA score at the start of CPFA.

Kaplan–Meier estimate of survival was constructed to compare 180-day survival between the patients treated with RCA and those treated with unfractionated heparin anticoagulation. Cox's F-test was used to test the difference in survival rates.

$p < 0.05$ value was considered statistically significant. Statistical computing and graphics were performed by Statistica v.10.1 (Statsoft, Tulsa, OK, USA).

3. Results

From January 2001 to December 2017, among the 212 patients who underwent RRT, 39 of them were additionally treated with CPFA (CPFA group), out of 1520 severe burn patients admitted to our Burn Center. We identified 87 patients (Control group) who were treated with RRT, but not CPFA, in the same period of time, and had showed no significant differences in terms of burn size, revised Baux score, gender, septic shock incidence, requirement of mechanical ventilation and time interval from admission to starting of CPFA or RRT (Table 1).

The overall observed mortality rate was 51.3% in the CPFA group and 77.1% in the Control group (p 0.004).

3.1. CPFA treatment

In the group CPFA, patients were aged 46.0 years (40.0–56.0; median, the 25th and 75th percentiles, range 14–81 years) with a burn size of 48.0% TBSA (35.0–60.0, range ≤ 85%). The median period between patients' admission and the onset of sepsis was 5.5 days (4.5–7.0). The median period between patients' admission and RRT start was 15.0 days (7.0–23.0).

The main reasons for starting an RRT treatment were fluid overload and oliguria (26 patients, 66.6%), followed by severe hyperkalemia (18 patients, 46.1%) and severe acidosis (16 patients, 42.0%), and uremic complications (3 patients, 7.6%). Most of patients of the CPFA and control groups were treated with potentially nephrotoxic drugs (aminoglycosides, colistin, vancomycin), and none of the patients underwent contrast-media procedures. No significant difference was found between the 2 groups in the use of nephrotoxic drugs, lactate levels, dose of vasopressors and SOFA score at the onset of treatment, time from shock to renal failure and overall RRT treatment duration (Table 1).

In 16 CPFA patients no comorbidities were found. In the remaining 23 patients, comorbidities included 6 cases of major psychiatric disorders, 5 cases of polytrauma, 3 cases of chronic hepatitis, 4 cases of chronic pulmonary obstructive disease

Table 1 – Demographic characteristics of 39 septic shock burn patients with AKI treated with CPFA (CPFA group) and of 87 burn patients treated with only RRT (Control group).[a]

	CPFA group[b]	Control group[c]	p
Patients (n)	39	87	–
In-hospital mortality (%, n)	51.3%, 20	77.1%, 67	0.004
Age (years)	46.0 (40.0-56.0)	61.0 (46.0-73.0)	0.003
Total body surface area (%)	48.0 (35.0-60.0)	40.0 (30.0-60.0)	0.250
Revised Baux score	111.2 (99.5-126.4)	121.7 (102.9-133.4)	0.118
Gender ratio (male%, n)	74.3%, 29	60.9%, 53	0.102
Septic shock (%, n)	100%, 39	91.9%, 80	0.337
Mechanical ventilation (%, n)	100%, 39	94.2%, 82	0.223
CPFA-RRT/RRT interval (days post-admission)	17 (9-25)	18 (10-28)	0.268
Septic shock/AKI interval (days)	5 (4-7)	5 (3-10)	0.938
CPFA-RRT/RRT duration (days)	5 (3-13)	10 (18-5)	0.111
Citrate anticoagulation (%, n)	51.3%, 20	75.8%, 66	0.012
SOFA score (at 1st day of treatment)	12 (10-14)	12 (10-14)	0.364
Lactate (mmol/l, at 1st day of treatment)	2.0 (1.4-2.5)	2.4 (1.5-3.7)	0.127
Norepinephrin (ug/kg/min, at 1st day of treatment)	0.40 (0.20-0.57)	0.40 (0.20-0.60)	0.762
Nephrotoxic drugs (%, n)	69.3%, 27	66.7%, 58	0.773
Aminoglycosides	56.4%, 22	52.8%, 46	0.708
Colistin	30.8%, 12	21.8%, 19	0.278
Vancomycin	30.8%, 12	26.4%, 23	0.610

Data are given as median (the 25th and 75th percentiles) or as percentage when appropriate. Student T-test or Fisher's exact test was done when appropriate.

[a] Control group (n 87) included all the burn patients treated with RRT from 2000 to 2017, with: (1) a time interval from admission to RRT ≥ 5 days, and (2) the range values of age of ≥14 and ≤81 years; and (3) %TBSA range of ≤85%.

[b] CPFA = coupled-plasma filtration adsorption with renal replacement therapy.

[c] RRT = renal replacement therapy alone.

(COPD), 6 cases of hypertension and 2 cases of diabetes. The overall prevalence of the above comorbidities in the CPFA group was not significantly different from that in the control group (p 0.4045).

Among a total of 70 positive cultures isolated from these patients' blood and other specimen sources the gram-negative strains were predominant (47/70 cultures). The top 6 micro-organisms were Acinetobacter Baumanni (21 specimens), Pseudomonas Aeruginosa (16 specimens), Staphylococcus Aureus MR (6 specimens), Candida spp. (6 specimens), Coagulase Negative Staphylococcus (5 specimens) and Sten-otrophomonas Maltophilia (4 specimens).

As shown in Table 2, non survivors were significantly older in the CPFA group (54 vs. 46 years, p 0.012), and had significantly higher SOFA score (13.0 vs. 11.0, p 0.005) and revised-Baux score (119.9 vs. 103.0, $p < 0.041$). No significant difference was found for burn size, days of CPFA and continuous RRT (CRRT), and CPFA dose. While searching for factors affecting survival in the CPFA group, we included the two following predictors in the multivariate analysis logistic model: SOFA score on the 1st day of CPFA, and age. Of these two predictors, SOFA score was significant (OR 2.016, 95% CI, 1.221 −3.326; $p < 0.004$), whereas p-value for age showed a trend towards significance (OR 1.065, 95% CI, 0.997−1.139; $p < 0.059$).

Fig. 1 shows the clinical trend of hemodynamics (mean arterial pressure (MAP), heart rate and norepinephrine requirement), metabolic indexes (plasma lactate and pH) and SOFA score for nonsurvivor and survivor patients before and after initiation of CPFA therapy. Lower values of MAP and pH, and higher norepinephrine requirements and lactate plasma levels were observed in nonsurvivors (Fig. 1). In survivors patients we observed a trend towards a progressive improvement of the hemodynamic and laboratory parameters. Nine patients died within the 2nd day of CPFA.

Regarding anticoagulation strategies, no significant differences were found for observed mortality rate, revised Baux score, SOFA score, CRRT days post-admission and number of CPFA sessions/patient performed, (Table 3). However, the patients that were treated with unfractionated heparin anticoagulation were younger and with higher burn size, whereas those that were treated with RCA were older ($p < 0.05$) and with lower burn size (p 0.06, Table 4).

Survival analysis by Kaplan−Meyer curves showed a trend towards a better survival for patients that were treated with RCA in comparison to those treated with unfractionated heparin, even though not significant (p 0.1583, Cox's F-test, Fig. 2).

Regarding CPFA flow rates, the session duration was significantly longer for patients treated with RCA, as well as the amount of effluent volume and net fluid removal. The median dose of plasma processed during CPFA, normalized to patient weight, was similar in the two groups (Table 4).

4. Discussion

Severe burn patients represent a specific model of AKI associated septic-shock in which the severity of the initial insult can be quantified in terms of burn size and revised Baux score, and the septic process develops predictably [12,16,25–29]. Moreover,

Table 2 – Characteristics, clinical parameters and outcome of non survivor and survivor patients treated with CPFA (CPFA group).

	Non survivor	Survivor	p
Patients (n)	20	19	
Age (years)	54 (43–71)	46 (30–51)	0.012
Total body surface area (%)	49 (35–65)	45 (35–60)	0.815
Revised Baux score	119.9 (105.9–131)	103.0 (94.8–120.5)	0.041
Gender ratio (male%, n)	65.0%, 13	76.1%, 16	–
Mechanical ventilation (%, n)	100, 20	100, 19	–
SOFA score (at 1st day of CPFA)	13 (12–14)	11 (9–11)	0.005
Cardiovascular	4 (4–4)	4 (4–4)	0.547
Respiratory	3 (2–3)	2 (1–3)	0.031
Hematologic	1 (0–2)	0 (0–1)	0.045
Liver	2 (1–2)	1 (1–2)	0.147
Citrate anticoagulation (%, n)	45.0%, 9	57.8%, 11	–
CPFA (sessions)	3.5 (1.5–7)	6 (4–10)	0.205
CPFA dose (l/kg/day)	0.179 (0.161–0.196)	0.171 (0.138–0.180)	0.135
CRRT[a] (days)	10.5 (3–17.5)	10 (7–20)	0.892
CRRT interval[a] (days post-admission)	16.5 (8–24.5)	18 (13–28)	0.907

Data are given as median (the 25th and 75th percentiles) or as percentage when appropriate. Student T-test or Fisher's exact test was done when appropriate.

[a] Days of CRRT are referred to days of treatment of only CRRT done before or after the cycle of CPFA-RRT days.

despite the improvements of supportive intensive care and the optimization of dialytic techniques, AKI in burn sepsis is still associated with a high risk of death [6–16].

It has been hypothesized that CPFA in burn patients could exert a beneficial immunomodulatory effect [14], being able to remove exogenous and endogenous inflammatory mediators through a plasma adsorption mechanism [1–3]. Nevertheless, there is no clear demonstration of a survival benefit from CPFA, so far. However, very few studies have addressed the clinical impact of CPFA on mortality rates, and the enrolled patients had septic shock of multifactorial etiology [5]. The selection of patients may be crucial for demonstrating the efficacy of the treatment. Even if it was recently shown that two sessions of CPFA in severe burn patients, in addition to routine treatment, significantly decreased the level of different cytokines [30], no study has addressed the issue of CPFA clinical efficacy in a selected and specific population, such as septic shock severe burn patients.

Considering the possible benefits and, at the same time, the lack of evidence, we decided to introduce CPFA as an

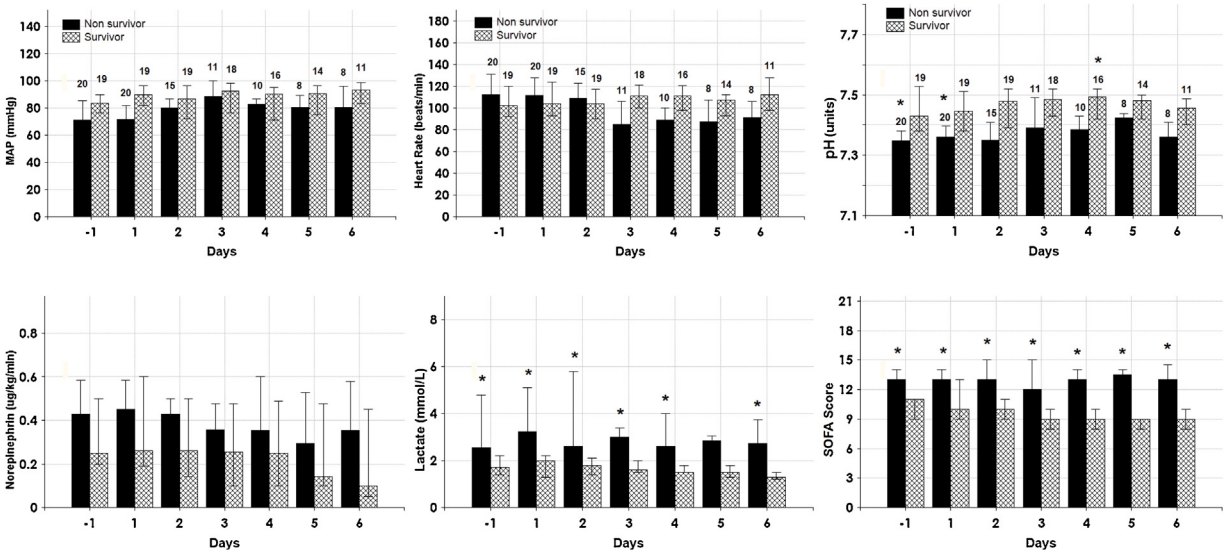

Fig. 1 – Outcome of MAP, heart rate, norepinephrine requirement, pH, blood lactate and SOFA score in the first six days of CPFA for Nonsurvivor (n 20 patients) and Survivors patients (n 19 patients). Data were taken at the start of CPFA day session. Data of Day 1 were the baseline data at time 0 of CFFA course. The number on the columns indicates the number of considered cases at each time. The Nonsurvivor patients were: 20 at day 1, 15 at day 2, 11 at day 3, 10 at day 4, 8 at day 5, and 8 at day 6. Data are given as median (the 25th and 75th percentiles). ANOVA and post-hoc analysis with Newman–Keuls multicomparison test was done between Nonsurvivor and Survivors patients (*$p < 0.05$). MAP = mean arterial pressure.

Table 3 – Demographic characteristics of 39 severe burn septic shock patients undergoing CPFA (CPFA group). Data were given according to anticoagulation protocol with Citrate (n 20 patients) and Heparin (n 19 patients).

	Citrate-CPFA			Heparin-CPFA			
	All	Dead	Alive	All	Dead	Alive	p[a]
Patients (n)	20	9	11	19	11	8	0.314
In-hospital mortality (%)	45.0 %	–	–	61.1 %	–	–	–
Age (years)	50.5 (43–62)	55 (46–78)	46 (40–55)	44 (31–56)	45 (37–60)	37 (40–47)	0.049
Total body surface area (TBSA,%)	45 (35–52.5)	45 (35–55)	45 (35k50)	56 (40–65)	50 (40-80)	58 (42–60)	0.062
Revised Baux score	108 (99–122)	114 (103–126)	104 (99–121)	117 (90–131)	124 (108-138)	102 (88–116)	0.756
SOFA score (on the 1st day of CPFA)	13.0 (9–13)	13.0 (12–15)	10.5 (9–13)	11.5 (10–14)	13.0 (11–14)	10.5 (9–11)	0.929
Gender ratio (male%, n)	70.0%, 14	44.4%,4	90.9%, 10	78.9%, 15	81.8%, 9	75.0%, 6	0.397
Mechanical ventilation (%, n)	100%, 20	100%, 10	100%, 10	100%, 19	100%, 11	100%, 7	–
CRRT interval (days post-admission)	18.5 (9–29.5)	21 (7–28)	18 (9–31)	15 (9–21)	12 (8–21)	17 (14–24)	0.387

Data are given as median (the 25th and 75th percentiles).
[a] Student T-test or Fisher's exact test was done between Citrate (all cases) and Heparin (all cases) anticoagulation protocol when appropriate.

adjunctive therapy only for severe burn patients with a poor prognosis, such those suffering from septic shock with multi organ failure sustained by multi-drug resistant bacterial strains not or poorly responsive to antibiotic therapy.

In the CPFA group the mortality rate was 51.3%, lower than the mortality rate in the control group treated only with RRT, and better in comparison to the literature data [6–13,16]. This result suggests that CPFA in burn patients with severe septic shock and concomitant AKI could provide an actual benefit on the outcome when compared to standard CRRT treatment.

We applied logistic regression analysis on our data, searching for factors that help predict the survival of patients treated with CPFA. We found that the SOFA score was the only significant parameter, whereas the age was near significance. As also suggested by the significantly higher value in nonsurvivors than in survivors, the SOFA score (Table 2 and Fig. 1) confirmed to be a reliable predictor of the outcome for burn patients [24,31,32]. In the same way, the observed high lactate levels in the first four days of CPFA, when mortality peaked (see Fig. 2) reflected the fatal outcome and confirmed lactate as a strong predictor of mortality in septic shock burn patients [33]. As shown in Fig. 1, the CPFA patients of both groups had slightly elevated levels of lactate, while having an extremely high mean SOFA score of >12. This puzzling discrepancy could be due to some specific conditions of burn patients, such as infection and organ dysfunction lasting a long time, the pathogenesis sustained by different microorganisms and the fluctuating course of infective process. In addition, we analyzed the presence of comorbidities [32,33]. We did not find a difference of overall comorbidities prevalence between the two groups, thus making the comparison reliable.

As expected, the patients of both groups experienced an intensive use of potentially nephrotoxic antibiotics. Therefore, the AKI pathogenesis of our patients was likely to be multifactorial. Besides immunological and infectious factors [29], AKI reflected also a direct tubular antibiotic toxicity, and both systemic and local hemodynamic derangements.

Table 4 – CPFA group flow rates according to anticoagulation protocol with Citrate (n 20 patients) and Heparin (n 19 patients) subgroups.

	All	Citrate-CPFA	Heparin-CPFA	p[a]
CPFA sessions	238	128	110	–
Sessions (no./patient)	5 (2–8)	5 (2–10)	5 (3–7)	0.945
Duration of CPFA session (hours)	8.0 (7.0–9.0)	8.0 (7.0–10.0)	7.5 (7.0–8.0)	0.005
Hemorrhagic episodes	6/238	0/128	6/110	0.005
Catheter-related complications	7/41	2/18	5/23	0.327
Hypersensitivity reactions	0/238	0/110	0/128	–
Blood flow rate (ml/min)	150 (140–160)	150 (140–165)	150 (150–160)	0.654
Circuit citratemia (mmol/l)	–	3.9 (3.4–4.5)	–	–
Unfractionated heparin (Units/hour)	–	–	900 (750–1200)	–
Effluent volume (l/session)	22.5 (19.5–27.0)	25.2 (21.6–33.6)	21.0 (18.0–24.0)	0.005
Net fluid removal (l/session)	0.20 (0.00–1.10)	0.70 (0.00–1.10)	0.20 (0.00–0.85)	0.024
Plasma-treated (l/session)	12.2 (10.4–14.6)	12.6 (10.4–16.3)	12.1 (10.1–13.4)	0.006
Plasma-processed dose (l/kg/day)	0.175 (0.144–0.198)	0.176 (0.144–0.202)	0.174 (0.145–0.196)	0.854

Data are expressed as median (the 25th and 75th percentiles).
[a] Student T-test or Fisher exact test was done between Citrate and Heparin groups when appropriate.

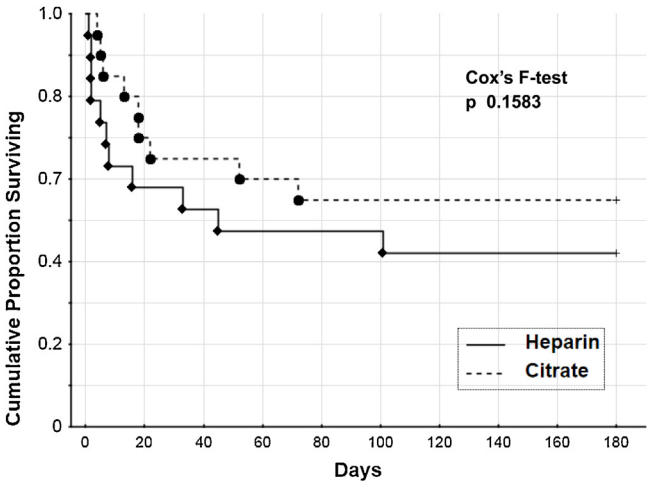

Fig. 2 – Survival analysis by Kaplan–Meyer curves for the Citrate-CPFA (n 20 patients) and Heparin-CPFA (n 19 patients) groups.

We further explored some technical aspects of the CPFA technique. Specifically, we wanted to see if the anticoagulation strategy adopted in delivering CPFA could influence the efficacy and safety of the treatment. The patients treated with unfractionated heparin anticoagulation and those treated with RCA had similar characteristics, even tough patients treated with unfractionated heparin coagulation were younger and had higher burn size. The observed mortality did not significantly differ between the two groups, even if the Kaplan–Meyer curves of survival showed a better trend for patients treated with RCA strategy (Cox's F-test p 0.1583). However, as previously described in continuous extracorporeal treatment [13,17,18], during regional unfractionated heparin anticoagulation hemorrhagic events were more frequent.

In the present paper we reported our clinical experience with a new treatment option for a specific ICU population, such as burn patients with septic shocks and poor outcome, and this could be the strength of our study, and likely one possible reason for the positive results. The improved survival rate is indeed far from being conclusive and should be considered as a starting point for further studies. CPFA in burn patients with severe septic shock and concomitant AKI could provide an actual benefit on the outcome when compared to standard CRRT treatment. According to other experiences, these data also suggest that the actual benefit demonstration of a new treatment option in ICU patients is deeply related to the choice of appropriate patients, with appropriate indications [34].

We recognize that our study has some limitations. First, severe burn patients suffer from a complex condition, and they undergo multiple interventions. Isolating the effect of a single treatment on the outcome could be impossible. Secondly, the number of subjects is limited in such specific population, and treated over an extended period of time when comprehensive burn care measures and team expertise have improved. Thirdly, as suggested by the high number of deaths in the first 48 h, the mortality rate could have been reduced with an earlier CPFA treatment. This consideration was also supported by the strong correlation of the SOFA score as a good predictor of fatal outcome.

5. Conclusion

CPFA treatment for burn patients with AKI-RRT and septic shock, sustained by bacterial strains non- or poorly responsive to therapy, was associated with a lower mortality rate compared to RRT alone. However, further research, such as large prospective studies, is required to clarify the role of CPFA in the treatment of burns with septic shock and AKI-RRT.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the City of Health and Science of Turin (dossier n. CS2/908).

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests and conflict of interest

The authors declare that they have no competing interests and/or conflict of interest.

Funding

This work was supported by a grant to FM from the Ministero dell'Istruzione, Universita' e Ricerca (MIUR, ex 60%), Italy. The authors declare no financial interest.

Authors' contributions

FM and ZH conceived the study, collected, analyzed and interpreted the data, and elaborated the manuscript. VM, AP,

AM, and DB performed the enrollment of patients in the study. LB, MB, and MS supervised the study, and ND corrected the final version of the manuscript. All authors read and approved the final version of the manuscript.

We state that the results presented in this paper have not been published previously in whole or part, except in abstract format.

Acknowledgments

The authors wish to thank Dr. Luisa Tedeschi and all colleagues for their valuable help in proofreading.

REFERENCES

[1] Ronco C, Brendolan A, d'Intini V, Ricci Z, Wratten ML, Bellomo R. Coupled plasma filtration adsorption: rationale, technical development and early clinical experience. Blood Purif 2003;21:409–16.
[2] Tetta C, Gianotti L, Cavaillon JM, Wratten ML, Fini M, Braga M, et al. Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock. Crit Care Med 2000;28:1526–33.
[3] Ronco C, Brendolan A, Lonnemann G, Bellomo R, Piccinni P, Digito A, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med 2002;30:1250–5.
[4] Formica M, Olivieri C, Livigni S, Cesano G, Vallero A, Maio M, et al. Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock. Intensive Care Med 2003;29:703–8.
[5] Livigni S, Bertolini G, Rossi C, Ferrari F, Giardino M, Pozzato M, et al. GiViTI: gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine). Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomized controlled clinical trial. BMJ Open 2014;4(January (1)):e003536.
[6] Leblanc M, Thibeault Y, Querin S. Continuous haemofiltration and haemodiafiltration for acute renal failure in severely burned patients. Burns 1997;23:160–5.
[7] Holm C, Horbrand F, von Donnersmarck GH, Muhlbauer W. Acute renal failure in severely burned patients. Burns 1999;25:171–8.
[8] Tremblay R, Ethier J, Querin S, Beroniade V, Falardeau P, Leblanc M. Veno-venous continuous renal replacement therapy for burned patients with acute renal failure. Burns 2000;26:638–43.
[9] Chung KK, Lundy JB, Matson JR, Renz EM, White CE, King BT, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. Crit Care 2009;13(3):R62.
[10] Soltani A, Karsidag S, Garner W. A ten-year experience with hemodialysis in burn patients at Los Angeles County + USC Medical Center. J Burn Care Res 2009;30:832–5.
[11] Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. Intensive Care Med 2010;36:915–25.
[12] Palmieri T, Lavrentieva A, Greenhalgh DG. Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. Burns 2010;36:205–11.
[13] Mariano F, Tedeschi L, Morselli M, Stella M, Triolo G. Normal citratemia and metabolic tolerance of citrate anticoagulation for hemodiafiltration in severe septic shock burn patients. Intensive Care Med 2010;36:1735–43.
[14] Linden K, Stewart IJ, Kreyer SF, Scaravilli V, Cannon JW, Cancio LC, et al. Extracorporeal blood purification in burns: a review. Burns 2014;40:1071–8.
[15] Chung KK, Coates EC, Smith Jr. DJ, Karlnoski RA, Hickerson WL, Arnold-Ross AL, et al. Randomized controlled evaluation of high-volume hemofiltration in adult burn patients with septic shock and acute kidney injury (RESCUE) investigators. High-volume hemofiltration in adult burn patients with septic shock and acute kidney injury: a multicenter randomized controlled trial. Crit Care 2017;21(1):289, doi:http://dx.doi.org/10.1186/s13054-017-1878-8.
[16] Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns 2017;43:898–908.
[17] Mariano F, Tetta C, Stella M, Biolino P, Miletto A, Triolo G. Regional citrate anticoagulation in critically ill patients treated with plasma filtration and adsorption. Blood Purif 2004;22:313–9.
[18] Mariano F, Morselli M, Hollo Z, Agostini F, Stella M, Biancone L. Citrate pharmacokinetics at high levels of circuit citratemia during coupled plasma filtration adsorption. Nephrol Dial Transplant 2015;30:1911–9.
[19] Dokter J, Meijs J, Oen IM, van Baar ME, van der Vlies CH, Boxma H. External validation of the revised Baux score for the prediction of mortality in patients with acute burn injury. J Trauma Acute Care Surg 2014;76:840–5.
[20] Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(1):204.
[21] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
[22] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. International sepsis definitions conference. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Med 2003;29:530–8.
[23] Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
[24] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
[25] Evidence-based Guidelines Group, A. B. A., & Paradigm Health Corporation. Practice guidelines for burn care. J Burn Care Rehabil 2001;(Supplement, v–xii):1S–69S.
[26] American Burn Association & American College of Surgeons. Guidelines for the operation of burn centers. J Burn Care Res 2007;28(1):134–41.
[27] ISBI Practice Guidelines Committee, Steering Subcommittee, Advisory Subcommittee. ISBI practice guidelines for burn care. Burns 2016;42:953–1021.
[28] European practice guidelines for burn care. 4th ed. . . . [Last accessed 31 July 2018] http://www.euroburn.org.
[29] Mariano F, Cantaluppi V, Stella M, Romanazzi GM, Assenzio B, Cairo M, et al. Circulating plasma factors induce tubular and glomerular alterations in septic burns patients. Crit Care 2008;12(2):R42.
[30] Meng A, Ren Y, Yang L, He L, Zeng S, Liu Q. Clinical study on continuous plasma filtration absorption treatment for burn sepsis. Zhonghua Shao Shang Za Zhi 2014;30:310–4.
[31] Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-

related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793–800.
[32] Belba MK, Petrela EY, Belba AG. Epidemiology and outcome analysis of sepsis and organ dysfunction/failure after burns. Burns 2017;43:1335–47.
[33] Lavrentieva A, Voutsas V, Konoglou M, Karali V, Koukiasa P, Loridas N, et al. Determinants of outcome in burn ICU patients with septic shock. J Burn Care Res 2017;38:e172–9.
[34] Vincent JL. Recent negative clinical trials in septic patients: maybe a good thing? Minerva Anestesiol 2015;81:122–4.