Clinical Evidence

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CPFA
Coupled Plasma Filtration Adsorption

Multiple Organ Dysfunction

Start

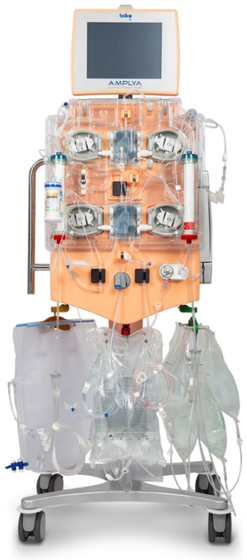
Patients affected by multiple organ dysfunction in acute care

The management of critically ill patients in the intensive care unit (ICU) is progressively increasing in complexity. Simultaneous dysfunction of various organs is frequent, leading to the so-called Multiple Organ Dysfunction/Failure Syndrome (MODS/MOFS)[1].

Critically ill patients may develop liver dysfunction in the context of MODS or may be affected by primary liver disorders. Liver dysfunction may become the trigger for several pathological pathways[1].

Rhabdomyolysis is a muscular disorder characterized by the leakage of skeletal muscle-cell contents (i.e., myoglobin) which can lead to life-threatening complications including severe hyperkalemia and hypocalcemia, acute kidney injury (AKI) and hypovolemic shock[2].

Critical clinical conditions involving excessive levels of myoglobin, bilirubin, biliary acids and systemic inflammatory mediators that may require plasma clearance are rapidly on the rise in acute care.



CPFA

CPFA[(A)] is a technique to remove myoglobin, bilirubin, bile acids and systemic inflammatory mediators.

The procedure begins with separating the plasma with a plasma filter, which allows for more removal of higher molecular weight mediators than typical hemofilters, and then passing the fluid through a resin cartridge. Hydrophobic adsorbent resin inside the cartridge permits fast and extensive adsorption of mediators while allowing reinfusion of albumin and amino acids. After passage through the resin, the purified plasma is returned to the patient. Associated with adsorption, a second clearance process uses hemofiltration to remove smaller toxins and control fluid balance.

A. CPFA treatment is carried out using Amplya medical device, that bears CE0123 in compliance with European Directive 93/42/EEC.

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As reported in literature the benefits of CPFA may include:

- Removal of **Bilirubin And Bile Acids** [3-5]
- Recovery of **Kidney Functionality** [5,10]
- Removal of **Myoglobin** [6-8]
- Restoration of the **Immune Response** [11]
- Removal of Pro- and Anti-**Inflammatory Mediators** [9]
- No Adsorption of **Albumin** [5,10]

Clinical Condition	Key Points	References
Acute or acute-on-chronic liver failure	Treatment with CPFA has been shown to be effective in removing bilirubin and bile acids in liver failure patients with a good safety profile, although it is a complex system in terms of technical application.	*Donati G, et al. J Nephrol. 2021;34(1):77-88*
Severe Rhabdomyolysis and AKI	The early use of CPFA in post-traumatic rhabdomyolysis has showed to prevent kidney damage. The serum creatinine and potassium values remained normal. Diuresis has always been present, and the blood levels of creatine kinase and myoglobin decreased rapidly.	*Pezzi M, et al. AGE Open Med Case Rep. 2019;7:2050313X19839529*
	All patients showed a significant reduction in creatine kinase and myoglobin blood levels, along with an improvement in renal function. During the treatment, all patients maintained good respiratory and hemodynamic stability and no complications were seen. Three patients survived and completely recovered after a rehabilitation period. One patient suddenly died on the 26th day for reasons not directly related to muscle injury or renal failure (cerebral hemorrhage).	*Pezzi M, et al. Case Rep Crit Care. 2017;2017: 5764961*
	Patient with AKI and severe rhabdomyolysis was treated with 5 sessions of CPFA, in combination with methylprednisolone. Rhabdomyolysis rapidly resolved with prompt recovery of the renal function.	*Lai Q, et al. Blood Purif 2015;40(3):218-22*
Liver transplantation and hyperbilirubinemia	After 3 treatment cycles of CPFA treatment, the bilirubin promptly decreased. Each treatment lowered the initial plasma level of bilirubin by about 40%	*Maggi U, et al. Transplant Proc. 2013;45(7):2715-17*
	CPFA allowed recovering an acceptable hemodynamic stability, and inotrope/vasopressor infusions were consequently reduced. The observed removal rate of conjugated bilirubin during CPFA was 47.8% after the first cycle, 53.8% after the second cycle and 59.3% after the third.	*Caroleo S, et al. Int J Artif Organs. 2010;33(10):749-52*

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Clinical Summary

TITLE Detoxification of bilirubin and bile acids with intermittent coupled plasmafiltration and adsorption in liver failure (HERCOLE study)

AUTHORS Donati G, Angeletti A, Gasperoni L, Piscaglia F, Croci Chiocchini AL, Scrivo A, Natali T, Ullo I, Guglielmo C, Simoni P, Mancini R, Bolondi L, La Manna G.

JOURNAL *J Nephrol.* 2021;34(1):77-88.

Background

The search for an extracorporeal purification system for acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF) is still a matter of debate. The pathophysiologic hypothesis informing the use of extracorporeal purification during ALF or AoCLF is the assumption that a vicious circle is initiated by the failing liver: during ALF or AoCLF toxins accumulate and cause direct damage to the liver itself, leading in turn to the faster accumulation of toxins.

Since most of the toxins that accumulate during liver failure are bound to albumin, their removal still represents a technological challenge.

A removal system able to break the molecular bonds between albumin and toxic substances is still missing and experiences with extracorporeal techniques for liver failure are currently limited.

Herein, the aim of the study is to apply the coupled plasma-filtration and adsorption (CPFA) extracorporeal depurative system to patients suffering from ALF or AoCLF in order to test its purifying capacity on both the main albumin-related toxins and the water-soluble toxins, as well as the biocompatibility of the system.

Methods

In this prospective observational study, authors enrolled patients with acute or acute-on-chronic liver failure (serum total bilirubin >20 mg/dL or Model for End-Stage Liver Disease (MELD) Score>20) hospitalized from June 2013 to November 2017.

The inclusion criteria for CPFA treatment were a diagnosis of ALF or AoCLF not responsive to the usual medical therapy and a rapidly progressive serum total bilirubin>20 mg/dL or MELD Score>20 at the time of enrollment.

Anticoagulation of the extracorporeal circuit was obtained with unfractionated heparin or with calcium-citrate loco-regional anticoagulation.

CPFA treatment was performed through a central venous catheter that was placed either in the internal jugular vein or in the femoral vein. Patients had intermittent treatments that lasted 6 h.

Blood samples were collected at the start of CPFA (t0) and then every hour until the end of the session (t60, t120, t180, t240, t300 and t 360) to assess bilirubin and bile acids variations. . Bilirubin and bile acids reduction ratios per session (RRs) were the main parameters for hepatic detoxification.

Results

Twelve patients with acute (n=3) or acute-on-chronic (n=9) liver failure were enrolled. Alcohol was the main cause of liver disease. Thirty-one CPFA treatments of 6 h each were performed, 19 with heparin and 12 with citrate. RRs was 28.8% (range 2.2–40.5) for total bilirubin, 32.7% (range 8.3–48.9) for direct bilirubin, 29.5% (range 6.5–65.4) for indirect bilirubin and 28.9% (16.7- 59.7) for bile acids. One patient received liver transplantation and 8/9 were alive at 1 year of follow-up. Three patients (25%) died: 2 during hospitalization and 1 for a cardiac event at 4 months of follow up with restored liver function.

Blood and plasma volume processed for each CPFA session were 54 L (range 72–41) and 8.2 L (range 3.8–11) respectively and the median ratio between plasma treated volume and patient weight was 0.10 L/kg/session (range 0.04–0.13). The median time between first and last CPFA session was 4.5 days.

After a single CPFA session both total and fractionated bilirubin and biliary acids significantly decreased. Bilirubin values 24 h after the end of the first CPFA session were significantly lower than the pre-CPFA values, despite the bilirubin rebound.

CPFA treatment was hemodynamically well tolerated.

Median value of mean arterial pressure remained stable during the CPFA session: 91.5 mmHg, 90.0 mmHg, 88.0 mmHg, 89.9 mmHg, 79.2 mmHg, 82.4 mmHg, 94.5 mmHg at t0, t60, t120, t180, t240, t300, t360 respectively (p>0.05).

Heart rate resulted stable during CPFA treatment. Vasoactive drugs were not administered to any patient.

All treatments were well tolerated. Safety was evaluated measuring several biochemical parameters in the serum: hemoglobin, white blood cells count, platelets, sodium, potassium and coagulation parameters variation before and after the CPFA session.

In this study 9/12 patients (75%) completed 1 year of follow-up: 8 recovered their basal liver function and 1 patient received an OLT. Three patients died: 2 during hospitalization and 1 at 4 months of follow-up for an acute cardiac event.

Conclusions

CPFA resulted to be effective in liver detoxification. Thus, it may be considered as a “bridge technique” both to the liver transplant and to the recovery of the basal liver function.

Clinical Summary

TITLE Early intensive treatment to prevent kidney failure in post-traumatic rhabdomyolysis: Case report.
AUTHORS Pezzi M, Giglio AM, Scozzafava A, Serafino G, Maglio P, Verre M.
JOURNAL *SAGE Open Med Case Rep*. 2019;7:2050313X19839529.

Background

Traumatic rhabdomyolysis is a clinical and biological syndrome secondary to lysis of striated muscle fibers resulting in extended musculoskeletal damage. An acute muscle damage causes the release of constituent elements of the sarcoplasmic reticulum, such as muscle enzymes, potassium, and myoglobin in plasma circulation; these conditions are at great risk of dangerous systemic complications for life such as hypovolemic shock, hyperkalemia, and acute kidney injury.

The authors describe the case of a patient who suffered a severe musculoskeletal and vascular trauma with elevated creatine kinase (CK) values and myoglobinemia treated early with coupled plasma filtration adsorption (CPFA) in order to prevent kidney damage, associated with volume replacement, loop diuretics, and correction of metabolic acidosis.

Case Reports

This clinical case concerns a patient, a 33-year-old male, who arrived at emergency room due to a severe crushing trauma that occurred during work involving the upper and lower right limbs.

The trauma caused an exposed fracture in the right lower limb in the medial third of the leg, which was treated surgically by intramedullary nail placement and screws for osteosynthesis. The clinical picture was more complex in the right upper limb where, after radiographic, tomographic, and angiographic examinations, a fracture of the proximal third of the humerus, with lesion and flow arrest of the axillary artery, was observed. Reconstruction was performed by the vascular surgeon using autologous venous grafts, while the fracture was treated with an external fixator. A fasciotomy of the right arm was also performed due to extensive collapse and muscle edema.

In intensive care, the patient was sedated with a continuous infusion of midazolam and remifentanil and subjected to artificial ventilation, continuous infusions of epinephrine at 0.07 mcg/kg/min plus dopamine at 5 mcg/kg/min, and broad spectrum-antibiotic therapy.

The patient began invasive monitoring of central arterial and venous pressure, fluid therapy at 300 mL/h, correction of metabolic acidosis with urine alkalinization, and furosemide as a continuous infusion at 20 mg/h such that for the first 6 days of hospitalization, the mean hourly diuresis oscillated between 3.2 and 3.7 mL/kg/h. Creatinine values were maintained below 0.9 mg/dL throughout the entire intensive care unit (ICU) admission. On admission to ICU and then, in the immediate post-operative period, the value of CK was 86,354 U/L, while the myoglobin level was 33,470 ng/mL. The CK value was checked every 12 h, while the myoglobin value was checked every 8 h.

CPFA was started after 6 h from the end of surgery, and after stabilization of the hemodynamic parameters. Six consecutive sessions of CPFA were performed for a duration of 12 h per session, maintaining a plasma target of 0.2 L/kg, blood flow (Qb) of 150 mL/min, and plasma flow (Qp) of 15% of blood flow (22.5 mL/min).

The levels of CK and myoglobin progressively decreased during the hours of treatment with CPFA. On day 5, the infusion of inotropic drugs was suspended, while on day 7, the process of weaning from mechanical ventilation began with a positive result and a return to spontaneous breathing. The patient was discharged on day 15 to the orthopedics department, where he continued his treatment.

Discussion

Intermittent hemodialysis does not effectively remove myoglobin in rhabdomyolysis due to the size of the protein. Conventional membranes easily remove small water-soluble molecules, such as urea (0.06 kDa) and creatinine (0.113 kDa), but not medium molecules such as myoglobin (about 18 kDa) and cytokines (~5–30 kDa). Instead, the continuous veno-venous hemofiltration or hemodiafiltration has shown some effectiveness in the removal of myoglobin, primarily with the use of super high-flow filters and high-volume ultrafiltration (convection). CPFA is an extracorporeal blood purification treatment that uses a plasma filter for separating plasma from blood, and then allows the passage of plasma through an adsorbent cartridge for removal of various non-specific mediators. Following purification, the plasma is returned to the blood: this can then go through a hemofilter for further blood purification by conventional hemofiltration in patients with acute renal failure.

The therapeutic goal of CPFA is to hit the excess of circulating mediators (both pro- and anti-inflammatory) in order to restore a normal immune function. CPFA combines the first stage of plasma separation and adsorption of cytokines, inflammatory mediators, and/or toxins, followed by the second stage of hemofiltration for volume control and removal of small water-soluble mediators in the range of the medium molecules such as myoglobin, triiodothyronine (FT3) and free thyroxin (FT4), and bilirubin. The maximum efficacy is obtained especially in the case of substances with high–medium molecular weight, such as myoglobin and cytokines.

Conclusions

The authors described the use of CPFA in post-traumatic rhabdomyolysis with renal damage, elevated blood levels of creatinine, and contraction or absence of diuresis. In the case described, the authors used CPFA early in order to prevent kidney damage, 6 h after the surgical revascularization along with the infusion therapy, diuretic, and correction of metabolic acidosis. The serum creatinine and potassium values remained normal. Diuresis has always been present, and the blood levels of CK and myoglobin decreased rapidly. The patient recovered without sequelae.

Clinical Summary

TITLE The use of coupled plasma filtration adsorption in traumatic rhabdomyolysis.
AUTHORS Pezzi M, Renda S, Giglio AM, Scozzafava AM, Tiburzi SP, Casella P, Iannelli F, Verre M.
JOURNAL *Case Rep Crit Care. 2017;2017:5764961.*

Background

Severe musculoskeletal injuries induce the release of sarcoplasmic elements such as muscle enzymes, potassium, and myoglobin in the systemic circulation. Among the various forms of rhabdomyolysis, the common pathophysiologic element is a rise in intracellular ionized calcium. The loss of transcellular calcium gradient causes a series of events that lead to cell death. If rhabdomyolysis is suspected, it is important to evaluate creatine kinase (CK) and myoglobin blood levels, since they represent the most sensitive markers of muscle injury. Changes in creatinine, potassium, sodium, blood urea nitrogen, total and ionized calcium, magnesium, phosphate, uric acid, albumin, and lactate blood levels also may be present. Other important investigations include acid-base balance evaluation, blood cell count, and coagulation tests. The main consequence of a massive release of myoglobin in the systemic circulation is acute kidney injury (AKI).

From November 2013 to December 2015, four patients with rhabdomyolysis were admitted at Anesthesia and Intensive Care Unit. All four presented raised serum CK and myoglobin levels and were promptly treated with fluid replacement, urine alkalinization, and forced diuresis to prevent myoglobin-induced renal damage.

Since low-flow hemodialysis does not allow the elimination of substances with a molecular weight exceeding 5 kDa, the removal of high molecular weight proteins such as myoglobin (17.8 kDa) requires coupled plasma filtration adsorption (CPFA). The patients underwent extracorporeal treatment with CPFA for 10 hours, followed by continuous veno-venous hemofiltration (CVVH) for 14 hours.

Case Reports

Case 1, Male, Age 19

The patient presented with a gunshot wound in his left lower limb, hemorrhagic shock, muscular disintegration, left popliteal artery occlusion, and multiple venous lesions. There was another gunshot wound in the skull with left temporal bone fracture and a retained bullet near the fifth cervical vertebral body.

The patient underwent vascular surgery approximately 8 hours after the traumatic event. Arterial vascularization was restored, fasciotomy of the left lower limb was performed, and continuous aspiration wound dressing was applied. After the surgery, the patient was intubated and under mechanical ventilation and inotropic support with dopamine. In the following 24 hours, fluid replacement was initiated with continuous monitoring of central venous pressure. Urine output was approximately 200 mL/h.

At 48 hours after the traumatic event, a further increase in levels of CK (14,790 U/L) and myoglobin (7,881 ng/mL) occurred. At this point, CPFA was initiated, alternating the first 10 hours of plasma adsorption with CVVH for the remaining 14 hours. Valid, spontaneous diuresis was present throughout the treatment, for a total of 72 hours. Given the positive evolution of the clinical course and laboratory values, CPFA was stopped. Plasma levels of myoglobin ranged from 7,881 ng/mL (before the first CPFA treatment) to 823 ng/mL (after the third CPFA treatment), with an average RR of 48%.

On the ninth day, the patient was transferred to the vascular surgery department for continued hospital care.

Case 2, Male, Age 55

The patient was brought to the emergency department with a crushed pelvis and lower limbs, after a road trauma involving a heavy vehicle. He presented with hemorrhagic shock due to

multiple pelvic girdle fractures, traumatic section of the urethra, retroperitoneal hematoma, left femoral fracture, L2 to L5 vertebral body fractures, and crush injury of the right lower limb. After suprapubic catheterization, the patient underwent external fixation of pelvic fractures and reduction of left femoral fracture. Fasciotomy was performed on the right lower limb and continuous aspiration dressing was applied. During the next 24 hours, with continuous monitoring of central venous pressure, fluid replacement was administered. The patient also needed inotropic support with continuous infusion of adrenaline and dopamine.

After suprapubic catheterization, the patient underwent external fixation of pelvic fractures and reduction of left femoral fracture. Fasciotomy was performed on the right lower limb and continuous aspiration dressing was applied. During the next 24 hours, with continuous monitoring of central venous pressure, fluid replacement was administered. The patient also needed inotropic support with continuous infusion of adrenaline and dopamine.

Given the onset of AKI, two sessions of hemodialysis were carried out at 48 and 72 hours after the trauma. At 96 hours, given the rising levels of serum CK and myoglobin, CPFA (alternated with 14 hours of CVVH) was started. The treatment lasted 96 hours, then was suspended due to clinical improvement and decrease of muscular and renal damage indices. Plasma levels of myoglobin ranged from 12,780 ng/mL (before the first CPFA treatment) to 1,516 ng/mL (after the fourth CPFA treatment), with an average RR of 37%.

During the following days, further improvement was observed. After one month of intensive care, the patient was transferred to a recovery department and then discharged.

Case 3, Male, Age 33

The patient presented with crush injury of both lower limbs caused by the overturn of a quad bike, with bilateral femoral and tibial fractures, right femoral artery section, and extended muscular damage of both lower limbs.

He initially was admitted to a spoke hospital, where traction was applied to his lower extremities. After approximately 12 hours, he was transferred for definitive treatment of bone, muscle, and vascular injuries.

Arterial revascularization of the right lower limb, reduction of fractures, and fasciotomy of both lower extremities were performed. After the surgery, the patient was brought to the ICU where he remained intubated and under mechanical ventilation.

During the following 24 hours, fluid replacement was administered with continuous central venous pressure monitoring. The patient also required inotropic support with continuous infusion of adrenaline and dopamine. Six hours after the surgical interventions, the right lower limb became ischemic again and was amputated. The left lower limb and the stump of the amputated limb were treated with a sealed continuous aspiration dressing. At 24 hours after the traumatic injury, the patient became anuric, so a three-hour hemodialysis session was performed. Since anuria persisted at 48 hours and laboratory exams showed further deterioration of renal function, CPFA therapy was started. Given the improvement trend, CPFA was suspended after 96 hours of treatment, and hemodialysis was restarted with a two-hour treatment on alternate days for three more days.

Plasma levels of myoglobin ranging from 12,757 ng/mL (before the first CPFA treatment) to 3,115 ng/mL (after the fourth CPFA treatment), with an average RR of 26%. During the following days, renal function restored completely, and both respiratory and hemodynamic parameters normalized. On day 26, the patient suddenly died due to cerebral hemorrhage.

Case 4, Male, Age 25

The patient was admitted to the emergency department after a 12-meter fall. He presented with multiple rib fractures, hemoperitoneum due to spleen rupture, multiple pelvic fractures, right femoral fracture, right ulnar fracture, extended muscular injury of the right upper and lower limb, and hemorrhagic shock. He immediately underwent splenectomy and bilateral chest drain positioning. Closed reduction of limb fractures was also performed. During the following 24 hours, the patient received fluid replacement therapy with close monitoring of central venous pressure. Due to hemodynamic instability, inotropic support with continuous infusion of dopamine was carried out.

In the ICU, the patient underwent pharmacological sedation, several transfusions of blood and hemoderivatives, mechanical ventilation, and antibiotic therapy.

On the second day of stay, after splenectomy, a sharp rise in muscle damage indices was observed, with CK levels of 30,389 U/L and myoglobin levels of 9,562 ng/mL and concomitant increase of creatinine value, while potassium levels remained stable. CPFA (with 14 hours of CVVH) was started, and treatment was carried out for a total of 72 hours with continuous improvement of serum CK and myoglobin levels and renal function parameters.

Plasma levels of myoglobin ranged from 9,532 ng/mL (before the first CPFA treatment) to 612 ng/mL (after the third CPFA treatment), with an average RR of 54%.

On the fifth day, an additional surgery was performed for internal fixation of femoral and elbow fractures and external fixation of pelvic fractures.

After 40 days of ICU stay, the patient was transferred to a rehabilitation center in good clinical condition.

Conclusions

The authors treated four patients with traumatic rhabdomyolysis with CPFA. CPFA was combined with CVVH. All patients showed a significant reduction in blood levels of CK and myoglobin, along with improvement in renal function. During treatment, all patients maintained good respiratory and hemodynamic stability and no complications were seen. Three patients survived and completely recovered after a rehabilitation period. One patient suddenly died on day 26 due to reasons not directly related to muscle injury or renal failure (cerebral hemorrhage).

Clinical Summary

TITLE Coupled plasma filtration adsorption in patients with a history of kidney transplantation: report of two cases.
AUTHORS Lai Q, Di Pietro V, Lesari S, Amabili S, De Luca L, Clemente K, Famulari A, Pisani F.
JOURNAL *Blood Purif.* 2015;40:218-222.

Background

Coupled plasma filtration adsorption (CPFA) has been extensively used to treat critically ill patients. The main benefit of using CPFA is its ability to remove a wide spectrum of molecules, thus positively modulating the inflammatory systemic framework to clear any imbalance between different types of sepsis mediators.

No clinical experience has been reported 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. In the present case, complete resolution of both rhabdomyolysis and acute kidney injury was observed.

Case Reports

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 (serum myoglobin zenith: 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 effectively remove circulating myoglobin; therefore, the patient was treated with five sessions of CPFA, in combination with IV administration of methylprednisolone (50 mg/day). Rhabdomyolysis rapidly resolved with prompt recovery of renal function (sCr at discharge: 0.9 mg/dL) and normalization of inflammatory markers. During the five days of treatment, no anticoagulation was required, and no bleeding occurred.

Conclusions

Several complex clinical conditions (i.e., rhabdomyolysis) may be effectively treated using CPFA, especially in cases of concomitant acute kidney failure.

The authors cannot provide strong evidence; however, their clinical experience suggests that CPFA can be safely offered to kidney transplant recipients when indicated. CPFA is effective not only in removing cytokines but also for removal of toxins such as myoglobin.

Pro-inflammatory substances such as cytokines are commonly involved in several specific pathological processes observed in the transplant setting, including delayed graft function, recurrence of primary renal disease, and uremic hemolytic syndrome.

Clinical Summary

TITLE Hyperbilirubinemia after liver transplantation: the role of coupled plasma filtration adsorption.
AUTHORS Maggi U, Nita G, Gatti S, Antonelli B, Paolo R, Como G, Messa P,Rossi G.
JOURNAL *Transplant Proc.* 2013;45(7):2715-2717.

Background

Liver transplantation (LT) has been the most revolutionary therapeutic option for hepatic failure in the past 50 years. Owing to the improved outcomes and extension of indications for this procedure, the small number of livers available appears to be the main obstacle to transplantation. Marginal livers (i.e., organs from a split or domino procedure, living donors, or donors with cardiac death) have been proposed to overcome the scarcity of standard organs. Although the aim is utilization of any available organ, the use of such grafts can expose the recipient to a risk of graft malfunction. Therefore, strategies have been developed to better match donor and recipient characteristics, one of which is the donor risk index. A spectrum of complication can arise early after LT using a marginal graft. These complications range from the so-called primary nonfunction to less defined malfunctions. A common post-transplantation finding is persistent hyperbilirubinemia.

In this article, the authors described two cases of patients affected by hyperbilirubinemia early after LT who were treated with coupled plasma filtration adsorption (CPFA). They described possible indications and preliminary results of this technique to treat disorders after LT.

Case Reports

Case 1

A 52-year-old woman with primary biliary cirrhosis (Model for End-Stage Liver Disease [MELD] score of 21) underwent a cadaveric whole LT in April 2012.

The hepatic graft was retrieved from a 75-year-old donor with 25% hepatic steatosis. Within the first week after LT, aspartate aminotransferase (AST) level reached a peak of 2.24 UI/L and alanine aminotransferase (ALT) reached 2.18 UI/L. Total bilirubin level was 21 mg/dL before transplantation, and it dropped to 9 mg/dL on post-operative day (POD) 1. On POD 7, bilirubin was 14.7 mg/d; after POD 11, it remained steadily at >20 mg/dL.

International normalized ratio (INR), which reached its worst values (INR = 2) on PODs 3 through 4, improved thereafter. On POD 12, gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) began to rise. The patient underwent a biopsy that was positive for acute rejection.

Because total bilirubin continued to increase, re-transplantation was considered. Meanwhile, the patient underwent three cycles of CPFA on PODs 27, 28, and 29. Soon after those treatments, the bilirubin dropped to 11 mg/dL (from 25.5 mg/dL on POD 18) and continued to decrease. The patient was discharged on POD 43 with a bilirubin level of 3 mg/dL and GGT of 1,000 UI/L. She was alive and well 6 months after LT, with a bilirubin level of 0.9 mg/ dL (normal values, 0.1 to 1.1), normal levels of AST and ALT, GGT of 101 UI/L (normal, 5 to 36), ALP of 150 IU/L (normal, 35 to 104), and INR of 1.0.

Case 2

A 64-year-old man with hepatitis B virus-related and alcoholic cirrhosis (MELD score of 15) underwent a cadaveric whole LT in February 2012. The hepatic graft was retrieved from a 62-year- old donor with no steatosis.

On POD 7, everolimus was initiated; tacrolimus was discontinued on POD 20. On POD 40, GGT and ALP levels began to rise, but a hepatic biopsy was not conclusive for acute rejection. Doppler ultrasound was normal. Bilirubin level began to rise but INR value remained in the normal range. Because chronic rejection was suspected, everolimus was discontinued and tacrolimus restarted. Because of concern about mechanical obstruction, retrograde cholangiography was performed on POD 60 to place a biliary stent. Thereafter, GGT and ALP decreased but bilirubin continued to rise up to 22 mg/dL with a normal INR value.

Tacrolimus concentrations remained high; on day 90, three cycles of CPFA were started. A subsequent biopsy suggested chronic rejection, and the patient was listed for re-transplantation. Soon thereafter, the bilirubin values began to decrease. The patient was discharged 97 days after LT. The bilirubin level continued to decrease to a steady range of 2 to 3 mg/dL. Over the following weeks, the patient steadily improved and was removed from the re-transplantation list.

Three months later, the patient developed Pneumocystis carinii pneumonia with acute respiratory distress syndrome. In addition, a hepatic artery thrombosis caused multiple hepatic abscesses. He died 7 months after surgery.

Note

The patient presented with crush injury of both lower limbs caused by the overturn of a quad bike, with bilateral femoral and tibial fractures, right femoral artery section, and extended muscular damage of both lower limbs. He initially was admitted to a spoke hospital, where traction was applied to his lower extremities. After approximately 12 hours, he was transferred for definitive treatment of bone, muscle, and vascular injuries. Arterial revascularization of the right lower limb, reduction of fractures, and fasciotomy of both lower extremities were performed. After the surgery, the patient was brought to the ICU where he remained intubated and under mechanical ventilation.

Results

This report of CPFA after LT described two cases, each using three treatment cycles and lasting 6 hours. Each treatment lowered the initial plasma level of bilirubin by about 40%.

Conclusions

CPFA was shown to lower plasma bilirubin in two patients with hepatic failure after LT. The results, however, depend on prognostic factors. CPFA deserves attention as a potential inexpensive, short-lasting treatment for hyperbilirubinemia after liver surgery or transplantation. Moreover, the effects of CPFA should be further studied to address inflammatory mediators in chronic rejection after LT or other immunologic disorders.

Clinical Summary

TITLE Coupled plasma filtration adsorption reduces serum bilirubin in a case of acute hypoxic hepatitis secondary to cardiogenic shock.
AUTHORS Caroleo S, Rubino AS, Tropea F, Bruno O, Vuoto D, Amantea B, Renzulli.
JOURNAL *Int J Artif Organs.* 2010;33(10):749-752.

Background

Hypoxic hepatitis (HH) is a frequent cause of acute hepatocellular damage and acute liver failure (ALF) in the ICU. Accordingly, an increase in serum bilirubin is a well-recognized risk factor for organ morbidity and mortality in the ICU. Therefore, ALF may be considered a signal of an upcoming multiple organ failure (MOF). Moreover, acute kidney injury (AKI) is one of the most common life-threatening complications in the context of MOF, and extracorporeal replacement therapies for AKI are widely used in ICU patients.

In this setting, more specific approaches have been proposed, such as high-volume hemofiltration (HVHF) and continuous plasma filtration adsorption (CPFA), to remove several pro- and anti-inflammatory mediators and to overcome the limitations of conventional continuous renal replacement therapies (CRRTs). The efficacy of CPFA combined with continuous veno-venous hemofiltration (CVVH) for the treatment of MOF in patients with ALF has been already described. This case report describes a significant reduction of conjugated bilirubin blood levels during CPFA instituted in a case of HH.

Case Reports

A 70-year-old woman was admitted to the ICU after coronary artery bypass grafting, aortic valve replacement, mitral valve repair, and tricuspid valve repair.

Preoperative echocardiography showed a left ventricular ejection fraction (LVEF) of 35%, while the SOFA score at ICU admission was 3. A modified Swan-Ganz catheter was introduced through the right jugular vein to monitor global hemodynamics.

Analgesia and sedation were maintained during the first 12 hours for clinical assessment. Weaning from mechanical ventilation was successfully completed thereafter. During the second postoperative day, low output syndrome and respiratory failure with associated signs of pulmonary congestion occurred. The echocardiography showed an LVEF of 25% with severe impairment of the left ventricular wall motion. These findings were suggestive of postoperative cardiogenic shock.

Dobutamine infusion, intra-aortic balloon pumping, and noninvasive mechanical ventilation were carried out as a first-line approach. However, norepinephrine infusion was required because of unresponsive hypotension. Concomitantly, renal failure occurred and was classified as AKI stage 2. Furthermore, a dramatic increase in serum aminotransaminase activity reaching 25-fold of the upper limit was observed. The rapid progression of jaundice, encephalopathy (Glasgow Coma score 10-12), hyperbilirubinemia (up to 38 mg/dL, almost exclusively conjugated), and coagulopathy (INR >3), in the absence of other causes for ALF, strongly suggested acute HH. A sequential organ failure assessment (SOFA) score >9 at the third postoperative day suggested a poor outcome.

Therefore, HVHF and CPFA were promptly instituted as extracorporeal supportive techniques as additional treatment to remove inflammatory mediators and to reduce fluid overload:

- HVHF, 2 cycles, 10 hours for each cycle
- CPFA, 3 cycles, 8 hours for each cycle

This extracorporeal support allowed the recovery of an acceptable hemodynamic stability, and inotrope/vasopressor infusions were consequently reduced. Aside from the beneficial renal and hemodynamic effects, a surprisingly significant reduction of serum conjugated bilirubin during CPFA was observed. The removal rate (RR) of conjugated bilirubin during CPFA was 47.8% after the first cycle, 53.8% after the second cycle, and 59.3% after the third. Therefore, plasma samples were collected concomitantly at the entrance and exit of the hydrophobic resin cartridge during the second and third cycles to ascertain if CPFA treatment might have been responsible for the observed reduction of serum bilirubin. Accordingly, the authors recorded an initial RR of 55.5% and a progressive reduction to 51.3% at the end of the treatment, with a mean RR of 53%.

None of these effects were observed during HVHF treatments. Although prompt medical and mechanical supports were instituted, the patient died of MOF on day 12 of the ICU stay..

Conclusions

The authors observed a significant reduction of the plasma concentration of conjugated bilirubin, achieving a mean RR of 53% during treatment. The plasma samples collected at the entrance and exit of the cartridge revealed an effective filtration of serum bilirubin. The observed RR was significantly higher than that reported for other conventional devices, such as the molecular adsorbents recirculating system (MARS), which have been designed to achieve an estimated RR of bilirubin about 28%.

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Disclaimer

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The Pre-assembled device for CPFA for Amplya and the Mediasorb Cartridge are included in KABL14P05 – KIT CPFA X AMPLYA procedure pack.

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Please refer to the devices and procedure pack Instructions for Use for complete instructions, contraindications, warnings and precautions.

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