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Clinical use of plasmafiltration coupled with adsorption

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Abstract: Coupled plasma filtration adsorption is an extracorporeal therapy that combines plasma separation and adsorption of inflammatory mediators and toxins, followed by hemofiltration to control volume overload and removal of small and medium-sized water-soluble mediators. Although it is not new, there are still doubts about its clinical role. Evidence indicates that the coupled plasma filtration adsorption is highly efficient in removing inflammatory molecules in sepsis. So far it has not been shown to reduce mortality, but it is possible to achieve a better hemodynamic benefit over convective therapies. On the other hand, the absorptive component makes it possible to purify larger mediators associated with causes of non-septic acute kidney injury, such as myoglobin, toxins associated with liver failure and others, allowing that coupled plasma filtration adsorption indications to be expanded to various clinical settings with a high inflammatory component, particularly when it is required to manage several organ dysfunctions simultaneously.

Key words: coupled plasma filtration adsorption; detoxification; sepsis; rhabdomyolysis; liver failure

1 Introduction

The hypothesis of in vitro purification techniques for the elimination of sepsis infarct mediators is that a decrease in the blood concentration of these compounds should determine a gradient conducive to their elimination from the tissues.[1] All of them require the passage of blood through an extracorporeal circuit containing one or more filters that exert their depurative effects, either by eliminating these substances or by sticking them to their surface.[2] The most common method is to use convection therapy to remove medium and high molecular weight media according to the pore size on the membrane. Other methods include plasma exchange[3] and the use of membranes with adsorption properties.[4] Comprehensive treatment can be achieved through coupled plasma filtration adsorption (CPFA),[5] which represents the combination of the above three technologies and is based on:

A. Plasma is separated from blood by plasma analyzer;

B. Subsequently, it is treated in a cylinder containing synthetic resin capable of adsorbing different body fluid media;

C. Purify the re-fusion of plasma to pass through the blood filter. (Figure 1)

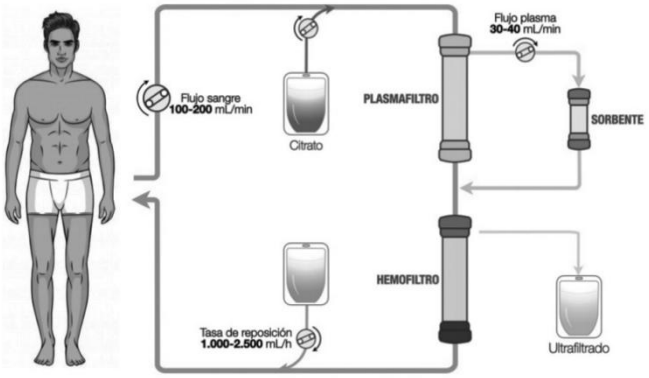


Figure 1. Coupled plasma filtration with adsorption (CPFA) circuit using citrate-based anticoagulation.

It is composed of a plasma filter (0.45m^2) and a high permeability polyphenyl blood filter (K_{uf} 41 ml/h/mmHg, area 1.4m^2). The plasma flow rate is 30 to 40 ml/min, and the plasma enters the Mediasorb® adsorption cylinder. This adsorbent contains 70 grams styrene polymer resin. The resin consists of mesoporous beads with a size of 50 to 100 μm; the average pore diameter is 30 nm, and the adsorption area is 700 m^2/g=50000 m^2.

During the process of CPFA, the adsorptive capacity of the resin is limited in time, but hemofiltration can continue even beyond its exhaustion, without the need to change the extracorporeal circuit. Moreover, unlike therapeutic plasma exchange, the patient's plasma is not discarded, making albumin or plasma infusion unnecessary (replenishment depending on the pathology for which plasma exchange was indicated).

In sum, CPFA is an extracorporeal clearance therapy, combining the first stage of plasma separation and adsorption of cytokines, inflammatory mediators and/or toxins, followed by the second stage of hemofiltration for control of volume overload and removal of small and medium-sized water-soluble mediators. This review will discuss the technical basis of this therapy and the rationality of treatment based on experimental, preclinical and clinical studies. Finally, recommendations for the use of CPFA will be made on the basis of existing evidence.

2 Treatment rationality of CPFA

Most cytokines and mediators in sepsis are too large to be effectively eliminated by convection or diffusion.[6] In addition to the molecular weight of the cytokines, the molecular size (the shape of the molecule as it rotates in solution) must also be considered, usually expressed as the Stokes-Einstein radius. This is why even in the case of high convection volume, the molecular size of these cytokines is not easy to pass through the pores of filtration.[7]

On the other hand, high permeability filters (high "cut of") allow the removal of larger cytokines, but have the disadvantage of being used only for short periods of time due to the risk of losing important physiological substances, mainly large amounts of albumin, even up to 15 grams in 4 hours.[8]

Hemoperfusion allows the selective binding and elimination of mediators or specific toxins and its main advantage is that the adsorbent matrix has a large surface area, reaching up to 1000 m^2/g.[9] Flow rates between 150 and 200 mL/min are used, which allows a larger volume of treated blood, but this is associated with a more limited adsorption, since the rapid flow causes several molecules, which would normally be adsorbed, to be carried away by the solvent flow. In addition, the whole blood and particularly the proteins, rapidly saturate the membrane, decreasing the efficiency of the adsorbent cartridge and generating cell activation.[10]

In contrast, plasma perfusion allows the use of lower flow rates (20-40 mL/min) without the risk of significant cell activation or membrane blockage, and by having a lower linear velocity, the contact time and adsorptive efficacy are

greater.[11]

These theoretical benefits were evaluated in experimental studies, in which the benefits of CPFA on changes in different mediators and biological variables in sepsis were demonstrated. The first in vitro study in an Escherichia coli endotoxin infection model showed that the adsorbent used in CPFA was superior to convection in eliminating various cytokines.[12] In a study of endotoxic shock in rabbits,[13] it was observed that the addition of an adsorbent cartridge improved survival at 72 hours when compared with isolated hemofiltration, which was independent of the lipopolysaccharide (LPS) load administered, since this cartridge does not adsorb LPS.

This reinforces the view that the observed benefits will come from higher adsorption rates of cytokines (Table 1). In this case, the biological activity of TNF-α in blood before and after the cartridge was analyzed, and a sharp drop was observed one hour after treatment.

Table 1. Molecules removed by coupled plasma filtration with adsorption (CPFA)

Absorbed by CPFA	TNF-α, IL-1α, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-16, IL-18, MIP-α, MIPβ, MCP-1, PCR, VEGF
Not absorbed by CPFA	Heparin, citrate, endotoxin, procalcitonin, albumin, ferritin
Uncertain	Immunoglobulin, drug

A few years later, Sykara et al. [14] used a pig septic shock model with feces inoculated intraperitoneally. The 16 animals received fluid intake and inotropic support until reaching a MAP above 65 mmHg, and then were randomly assigned to receive CPFA (n=8) or general hemodynamic support measures. In addition, CPFA can not protect the development of liver or lung dysfunction, and even aggravate the coagulation and oxidative stress disorder caused by sepsis. It is worth noting that the rabbit study showed a survival benefit 3 hours after a single CPFA treatment, while the pig study was not intended to assess a beneficial mortality rate 10 hours after a single CPFA treatment. The reason for this difference is still unclear. However, several possible explanations can be considered:

Firstly, in the study of Tetta et al. [13] the acute inflammatory insult caused by a large bolus of endotoxin and the absence of fluid resuscitation resulted in a pattern of hypovolemic shock that differs from the hyperdynamic polymicrobial shock model used in the swine model, in which a strict protocol of mechanical ventilation, fluid resuscitation, vasopressor support and blood glucose control was used.

Secondly, the effect of CPFA was studied in rabbits by pretreatment (30 minutes before endotoxin injection), while in pigs, CPFA was performed 12 hours after peritonitis induction. In other words, there are established signs of hyperkinetic shock, systemic infarction and microvascular changes of organ dysfunction. Therefore, it seems reasonable to think that the difference between the two models and the timing of blood purification strategies may become important in this case. This reasoning can be supported by evidence that the beneficial effects of hemofiltration on sepsis are less important if treatment starts late.[15-16]

Thirdly, the study of pigs is not divorced from reality, because it does not use antibacterial therapy, and the focus has not been excluded. This indicates that the application of this technology in humans has been very different. In humans, extracorporeal support therapy can only be considered after the basic measures package for septic shock.[17]

Of course, when interpreting the preclinical findings, we must take into account the main differences between the experimental model and human sepsis, because the observation of septic shock shows that the use of CPFA is related to the improvement of various clinical variables, such as the use of mean blood pressure (MAP) and vasopressin, [18-22] and the improvement of cardiac index and PaO_2/FiO_2.[23] However, all these variables tend to return to baseline during the

intervals between treatments, indicating that the benefits disappear at the end of each therapy. This "saw-tooth" trend has been replicated in clinical studies with CPFA, in which the sublingual microcirculation has been analyzed by using orthogonal polarization spectral imaging [24] and suggests that clearance of inflammatory mediators is much more efficient than hemofiltration or plasma alone, but that this effect may not necessarily be associated with a change in mortality.

The need to confirm previous encouraging results with an efficacy study led the GiViTi (Italian Group for the Evaluation of Intensive Care Interventions) to conduct a multicenter randomized clinical trial in patients with septic shock (COMPACT) with the main objective of evaluating mortality at 28 days or at hospital discharge, comparing patients treated with CPFA with standard treatment.[25] Diagnosis and treatment of septic shock was performed according to the 2012 Surviving Sepsis Campaign Criteria. The trial was stopped prematurely due to futility. The factors leading to this premature closure were mainly centered on technical problems (circuit coagulation), which resulted in about 50% of the patients included in the trial not reaching the target of 10 hours of treatment per day. In the protocol analysis, patients who received CPFA, and who achieved a treated plasma volume greater than 0.20 L/kg/day, showed a significant reduction in mortality (20%) compared to patients in the control group and to those patients who received a lower dose of treated plasma volume.

It is necessary to use new clinical trials to verify these data, so as to prove that the application of this technology can reduce the mortality rate by 20% under the above conditions. On this basis, the sample size was calculated. One of the trials was the Compact-2 study [26], which ended prematurely in October 2017 because it found that the early mortality (the first three days) in the intervention group increased (6/42, 12.5% vs 19/58, 32.8%; p=0.020), which did not reach the sample size set in the protocol (350 patients). The analysis is conducted on samples smaller than the predetermined sample size, so the statistical capacity is low. Subgroup analysis is likely to obtain distorted and unexpected results, because it is highly exposed to random maximum value, so low mortality in the control group must be considered, which obviously affects the analysis results. Other grouping analysis conducted by the authors should be considered in the same way. These results must therefore be carefully considered.

The second control trial was the ROMPA [27] study in Spain, which was closed prematurely in November 2017 due to external reasons of the trial itself. Only 49 patients were recruited at that time (30 in the control group and 19 in the intervention group); i.e., it reaches 26% of the predetermined sample size (190 patients), so the assumed contrast is very low (<30%). In this case, the ROMPA researchers did not find any mortality differences in the analysis of the three diseases (7/30, 23.6% vs 8/19, 40.6%; p=0.146), 28 (11/30, 46.7% vs 11/19, 57.9%; p=0.444); 90 days (19/30.63.3% vs 11/19, 57.9%; p=0.878) [28].

Therefore, we can say that the current evidence cannot prove that the application of CPFA under the conditions described in the respective agreements can reduce the mortality by 20%. Obviously, we cannot exclude minor benefits, and its analysis requires at least recalculation of the sample size.

It can be affirmed that the greatest effectiveness of CPFA is achieved when the plasma dose to be treated is high.[29] This goal may be difficult to achieve, because different factors help to reduce the effective time and effectiveness of the adsorber, such as blood coagulation, vascular access dysfunction and hemodynamic changes during cardiopulmonary bypass. However, appropriate patients selection and use of citrate regional anticoagulation may be the determining factor for better results.[30-32]

Table 2 summarizes the prescription and monitoring characteristics. In order to ensure the effectiveness of CPFA, blood anticoagulation must be vigorously considered to ensure the duration of cardiopulmonary bypass. Systemic anticoagulation with heparin is reserved for patients who already have this indication, such as those on ECMO. In these

cases, close monitoring with TTPa or ACT and ideal Antithrombin III (ATIII) levels should be maintained above 80%. If these ATIII levels are not reached or if it is not possible to measure them, ATIII or fresh frozen plasma administration can be considered before starting anticoagulation with heparin. On the other hand, if it is not possible to ensure adequate follow-up with these parameters or there is a risk of bleeding, regional anticoagulation should be preferred.

In clinical practice, at present, CPFA technology can only be carried out with the external support device named Amplya^{TM}(Acute Multi Thermal System, Bellco, Mirandola, Itali), which allows the use of regional anticoagulation in the mode of "auxiliary citrate", "free citrate", "protamine neutralizing heparin" and "mixed" (citrate plus low-dose heparin).

Our group prefers the auxiliary citrate mode, because the machine will automatically adjust the citrate concentration according to the patient's characteristics, changes in Qb, blood flow and results of ionic calcium. These changes must be monitored within 30 minutes, and then treated every 2 hours. This helps the clinical team to implement treatment, monitor and secure CPFA.

3 Indication of CPFA in clinical practice

Although the therapeutic rationality of CPFA is mainly based on sepsis, the resin in the plasma cartridge can also remove cytokines and mediators under other severe infarction conditions, as well as myoglobin, a variety of toxins and drugs under excessive conditions, thus expanding the number of indications of CPFA in normal clinical practice.[7]

There are still reasonable doubts about the specific instructions of CPFA and how to improve the results. The reason for this is that the best time to start treatment is not yet clear, and there is a lack of an acceptable biomarker to determine whether it will have additional benefits than another purification therapy. However, based on the current evidence, it is possible to propose the following clinical applications.

3.1 Multiple organ dysfunction in septic shock

The use of hypervolemic hemofiltration in sepsis has different clinical outcomes, and meta-analysis cannot prove that mortality has a substantial positive outcome.[33] However, this technology is still in use because it has a significant impact on hemodynamic components [34], which provides time for the sum of established treatments to help patients improve. However, for those with various organ dysfunction, continuous improvement still has limitations. This is partly due to the "dialogue" between institutions and the subsequent release of mediators, which led to the deregulation of other systems.[35] For these situations, improved methods are proposed, such as high "cut-off" membrane and adsorption technology.[36]

The application of CPFA in this type of clinical scenarios includes patients with septic shock plus severe renal and hepatic dysfunction, since it is possible to remove bilirubin and toxic fatty acids that generate nephrotoxicity when they are filtered by glomeruli and subsequently internalized in the proximal tubule by megalin-mediated endocytosis.[37] Even after the initial resuscitation phase is completed, the application of CPFA could decrease the risk of acute kidney injury (AKI). Castellano et al. [38] studied the pathophysiology of endotoxin-induced AKI. After infusing lipopolysaccharide into pigs, they observed acute tubulointerstitial fibrosis and endothelial dysfunction within 9 hours. However, by using CPFA for 6 hours in the early stage and by protecting the endothelial phenotype of capillaries and arteries around renal tubules, the occurrence of acute fibrosis can be significantly prevented. It is assumed that this benefit is achieved by significantly adsorbing lipopolysaccharide binding proteins from plasma in CPFA cartridges. Another common organ interaction occurs in acute respiratory distress syndrome (ARDS). More than 60% of ARDS patients have a incidence rate of LRA.[39] One of the explanations for this phenomenon is the excessive production of cytokines involved in lung kidney bidirectional injury, because the injury of renal tubule epithelium is conducive to the release of IL-6, which is related to the increase of alveolar capillary permeability, while ARDS may lead to renal medulla infiltration, which will cause additional damage to renal tubule cells.[40] The use of CPFA has shown a good effect in patients with ARDS, improving the commitment of

PaO_2/FiO_2 and lung parenchyma.[23, 41]

As previously described, there is no evidence to support the use of CPFA in septic shock to reduce mortality, but studies prior to clinical trials documented the possibility of benefits at other levels not as compelling as mortality, such as increasing MAP, decreasing inotropic support, and improving oxygenation.[18-23] On the other hand, we know that the benefits of CPFA depend on reaching a certain amount of therapeutic plasma, and have nothing to do with the time after the onset of hypotension.[29]

In view of these facts, it is necessary to consider new situations in which CPFA may be beneficial to patients with septic shock. At present, our organization is considering using CPFA in the following clinical situations:

According to the current standards of our institution, patients who have been treated with resuscitation program and diagnosed as hyperkinetic septic shock.

The average blood pressure was ≥ 65 mmHg, and there was enough $S_{at}O_2$. However, despite the initial resuscitation, a high dose of inoculum (noradrenaline ≥ 0.3 μg/k/min) was still required and/or perfusion parameters could not be improved (e.g. lactic acid ≥ 2 mm/L).

It has a good prognosis if extracorporeal support therapy is applied. That is, it has no compassionate indication.

It also has other organ dysfunction or pathology that can benefit from this combination therapy (such as liver dysfunction, capillary leakage, concurrent rhabdomyolysis, active autoimmune disease, severe poisoning).

3.2 Non infectious infarction syndrome with organ dysfunction

As with sepsis, there are various immune and tumor causes. The excessive and uncontrolled release of proinfarct cytokines (IL-6, resistin), [42-43] over expansion, anti infarct mediators (IL-10) and pathogen related and damage related molecular models (PAMPS) are out of control, leading to organ dysfunction and worsening clinical results, which may be due to poor regulation of pro infarct response.[44]

It is unreasonable to try to block a medium or a single pathophysiological pathway, because there are multiple pathways of inflammatory reaction, many of which are redundant. An example of this is the recent attempts to stop the exaggerated inflammatory response of patients with severe COVID-19 using tocilizumab, a drug that selectively blocks the IL-6 receptor, and whose results so far have been disappointing in most studies.[45] In addition, the use of immunosuppressants in this situation may increase adverse side effects in the short term, such as hepatotoxicity, neutropenia and thrombocytopenia [46], and on the other hand, the risk of serious infection in the long term.[47]

However, acute intensive elimination of a wide range of cytokines involved in this process, rather than a single cytokine, may be of great help to acute patients, because immune regulation is not expected to increase sustained immunosuppression in the medium and long term, thereby gaining benefits.[48-50]

In this way, CPFA will play an important theoretical role in patients with COVID-19 and multiple organ dysfunction. It has been observed in a group of these patients that when this phenotype occurs, the mortality may be higher, [51] which may be due to potential genetic conditions.[52] However, due to the lack of evidence in this regard, the application of CPFA in patients with COVID-19 is still theoretical, but this benefit will apply to patients with different causes, and these patients tend to converge in this common phenomenon.

3.3 Capillary leakage syndrome

In capillary leakage syndrome, a large number of pre infarction cytokines seriously damage the glucocorticoids of endothelial cells, thereby increasing permeability. Leakage and a large amount of plasma protein are lost to the stroma, leading to systemic edema, stubborn hypotension due to leakage and multiple organ dysfunction. Septicemia is the main cause. At present, there is no specific treatment method to effectively manage this situation, because the general support

personnel are poorly managed.[53] In severe and refractory cases, the use of hemodialysis with high cut of filters [54] and plasmapheresis [55] has been reported. Recently, the first case of CPFA was reported in a patient with severe and refractory capillary leakage associated with acute generalized exanthematous pustulosis, and good results were obtained.[56]

Early identification of capillary leaks and installation of CPFA may be a useful tool to avoid overuse of leaks. In these cases, the main purpose is to seek immune regulation under clinical conditions. In this case, even if there is no septicemia, the large release of cytokines is the main pathogenesis.

3.4 Liver dysfunction

After studying the adsorption characteristics of CPFA cartridges, it can be concluded that this technology is suitable for the purification of toxins in liver injury, so as to provide various clinical applications for patients with acute or chronic liver failure.[7]

Various studies have shown that besides effectively removing water-soluble and protein binding toxins, CPFA can also reduce bilirubin levels by 30% to 50% in each cycle.[57-58] The HERCOLE study [59] showed that CPFA was effective in the "detoxification" of patients with liver failure and is now considered a good "bridging technique" to liver transplantation or until recovery of baseline liver function. The regional citrate assisted anticoagulation mode and corresponding protocol monitoring (Table 2) provided by Amplya^{TM} allow the safe use of CPFA under these clinical conditions.[32, 59]

Table 2. Prescription and Monitoring of CPFA

Prescription	Choices	Monitoring
Time	6 hours 10 hours	Liver failure without renal failure Septicemia with or without renal failure, poisoning, and molecular clearance in immune diseases.
Blood Flow	100-150 mL/min	Mean blood pressure Circuit pressure and alarm Vascular access
Plasma Filtration Fraction	3% up to the 2nd hour 15% up to the 4th hour >18% up to term	Plasma filter transmembrane pressure < 20 mmHg Cross joint pressure < 150-180 mmHg In cases of liver failure, omit blood loss alarm in cases of severe hyperbilirubinemia.
Convective Flow	Up to 25%	Transmembrane pressure of blood filter
Automatic Solidification	Systemic heparin (10,000 IU at priming and then 10-15 IU/kg/h maintenance. Local anticoagulation with heparin and protamine Citrate assisted local anticoagulation Citrate free local anticoagulation*	 TTPa (40-60 seconds) ACT (140-200 seconds) Antithrombin III>80% Total calcium calcium ion lactic acid Arterial blood gas Sodium, potassium, chlorine, magnesium

(*) In the "free citrate" mode, the management of citrate and calcium solution is controlled by the operator. The machine does not monitor or adjust any parameters related to anticoagulation, and the treatment team needs to perform protocol monitoring and control.

3.5 Rhabdomyolysis

The sensitivity of myoglobin level to the diagnosis and monitoring of rhabdomyolysis is low, but it is related to glomerular and renal damage. Traditional hemodialysis and convection therapy cannot effectively eliminate it.[60] On the other hand, the CPFA adsorption cartridge has a great affinity for this molecule. After repeated CPFA treatment, it has proved to be very effective in different cases of severe rhabdomyolysis. In these cases, renal function and other dysfunction have been improved.[61-62] In most cases of severe rhabdomyolysis, management focuses on providing fluid, urine alkalization and correcting water electrolyte disorders, while renal replacement therapy is used in cases of severe renal failure.[60] When it is very urgent to clear myoglobin, the patient is at high risk of oliguric AKI, or the internal environment changes significantly, as well as other device dysfunction, CPFA is required, because the addition of blood filtration in this technology can ensure adequate myoglobin adsorption, the elimination of inflammatory mediators, and the management of the internal environment.

3.6 Rescue of self injuring nervous system diseases

In all antibody-mediated neurological disorders, treatment should be early and aggressive because of their rapid progression and risk of permanent neurological disability. This translates into multimodal immunotherapy, which often includes the use of immunoglobulin or plasma exchange.[63] The advantage of the latter is to eliminate immune complexes and cytokines, as well as changes in the number of immune cells and changes in the functions of regulatory T lymphocytes and natural killer cells.[64] This physiological basis supports that theoretically the addition of an adsorptive method would be more effective than plasma filtration alone. For example, the combination of immunoadsorption with plasma exchange has been shown to provide better clinical outcomes and shorter hospital stays in cases of myasthenia gravis.[65] On the other hand, a randomized single-center study showed that immunoadsorption had a higher response rate than plasmapheresis.[66]

Fabri et al. [67] reported a complex case of Guillain-Barré after influenza vaccination with refractoriness to initial therapy and complications resulting in multiple organ dysfunctions and shock. After the application of CPFA, it gradually improved, and there was no motor or sensory disorder at discharge.

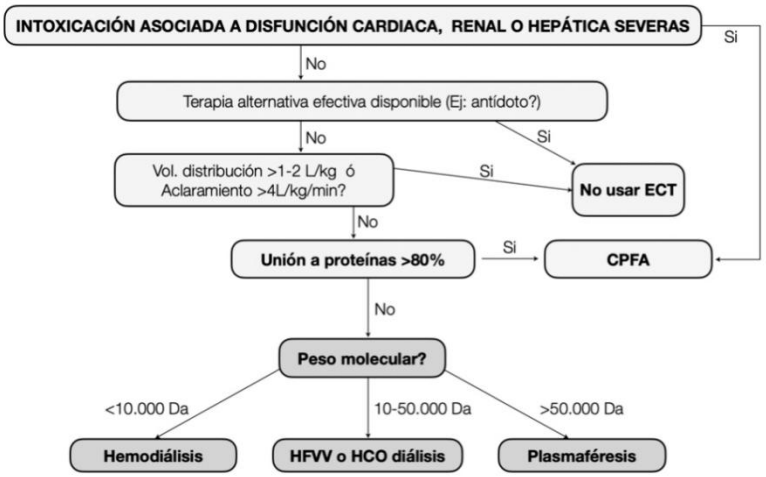
If the patient suffers from serious autoimmune nervous system diseases, such as severe autoimmune encephalitis, CPFA can be considered when drug resistance appears in first-line multimodal immunotherapy or nervous system diseases are related to other organ dysfunction.

3.7 Severe poisoning

In the face of severe poisoning, when there is no antidote and the endogenous clearance rate is low, external treatment is considered.[68] Hemodialysis is the most commonly used technology, especially if the molecular weight of toxic substances is low, they are soluble in water and have low binding power with protein. In addition to the pharmacokinetics of toxic substances, when organ dysfunction is also found, adsorption technology will become useful, especially due to heart failure, renal failure or liver failure, resulting in impaired excretion function.[69]

CPFA should be considered in the case of exogenous poisoning and secondary organ dysfunction of drugs or toxins with high protein binding (> 80%). In some cases, it is necessary to quickly remove substances that displays as endogenous toxins, as described in the case of thyroid storm related to amiodarone poisoning, in which it is observed that the resin can effectively adsorb, triiodothyronine (T3) and free thyroxine (T4) are also amiodarone with high protein binding.[70]

If the protein binding is less, the molecular weight of the drug will determine the type of treatment, which may be hemodialysis, hemofiltration or plasma exchange. (Figure 2)



ECT: Extracorporeal Therapies;
CPFA: Coupled Plasma Filtration with Adsorption;
HFVV: Hemofiltration Venous-Venous;
HCO: Hemodialysis with high cut of.

Figure 2. Phased approach to start extracorporeal treatment in poisoning management

4 Conclusion

CPFA is very effective in clearing infarct molecules in sepsis. Although it has not been proved to reduce mortality so far, it is possible to obtain higher hemodynamic benefits than convective therapy. On the other hand, the addition of adsorption components can purify larger cytokines and mediators related to non septic LRA causes, such as myoglobin, toxins related to liver dysfunction, and elimination of toxins or drugs, thus extending the indications of CPFA to various clinical situations with a large number of infarct components, especially when multiple organ dysfunction needs to be treated at the same time.

The main difficulty of this technology is related to the necessary conditions to ensure that the volume of plasma to be processed is 20%. This means that the patient must remain stable during the connection and have adequate vascular access.

In insufficiently resuscitated patients or patients with dysfunctional vascular access, it is highly likely that therapy should be discontinued before the plasma target is achieved. Similarly, the use of regional anticoagulation allows the circuit to last the proposed time, but this requires a highly qualified and coordinated clinical team to respond 24 hours a day to alerts that may arise during treatment. Fortunately, the "citric acid assisted" system provided by Amplya™ equipment is conducive to protocol monitoring, which improves patient safety and reduces potential errors in machine parameter adjustment.

Conflicts of interest

The author declares no conflicts of interest regarding the publication of this paper.

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