Review Article
Volume 9:3, 2020
DOI: 10.37421/aim.2020.9.298

Alternative and Integrative Medicine

ISSN: 2327-5162 **Open Access**

A Comparative Analysis between Nanomembrane-Based Therapeutic Plasmapheresis and Other Plasmapheresis Methods and Their Potential Use during the COVID-19 Pandemic

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Abstract

During a plasmapheresis session, a centrifugation device or membrane-based replacement equipment removes a portion of blood plasma, and separates pathologic macro-molecules from the patient´s blood for therapeutic purposes. The removed substances include alloantibodies, autoantibodies, cytokines, toxins, monoclonal proteins, lipoproteins and other plasma components. The American Society for Apheresis (ASFA) reviews its clinical indications for various medical fields, such as hematology, oncology, neurology, rheumatology and nephrology. In addition, a relevant aspect about plasmapheresis is that it is an effective adjuvant treatment for acute liver failure, peripheral vascular disease, Guillain-Barré syndrome, sepsis, Disseminated Intravascular Coagulation (DIC) and Thrombotic Thrombocytopenic Purpura (TTP), which are all possible complications of Coronavirus Disease 2019 (COVID-19). Different organizations around the world have made much progress in plasmapheresis´ biomedical engineering. One of such advances is the creation of more practical equipment and of a filter for nanomembrane-based therapeutic plasmapheresis. The nanopores of this multi-membrane filter allow for a more specific and less traumatic blood filtration. This process requires a single needle insertion and functions with an extracorporeal volume of only 70 mL, thus reducing risks and allowing its use even for pediatric patients. Other advantages include its relative lower cost, the short duration of treatment and the fact that donor plasma as a replacement fluid is optional, reducing in that way the risk of infection and allergic reactions. This comparative review will focus on these advantages and also on the aforementioned potential applications of nanomembrane-based therapeutic plasmapheresis for some of the complications of COVID-19.

Keywords: Nanomembrane-based plasmapheresis • Apheresis • Membrane plasmapheresis • COVID-19 • Coronavirus disease

Abbreviations: ASFA: American Society for Apheresis • DIC: Disseminated Intravascular Coagulation • COVID-19: Coronavirus Disease 2019 • TTP: Thrombotic Thrombocytopenic Purpura • cTPE: Centrifugal Therapeutic Plasma Exchange • mTPE: Membrane Therapeutic Plasma Exchange

Literature Review

Plasmapheresis

The literal meaning of plasmapheresis is "removal" or "subtraction" of plasma. Also known as therapeutic plasma exchange, it differs from hemodialysis in its mechanism of action and its desired effects. The mechanism of hemodialysis is the filtration of the patient´s blood by the chemical manipulation of its solutes with an exogenous fluid, through a membrane. In this way, it removes urea and other waste products, but in the process it also removes some beneficial substances such as vitamins. Plasmapheresis, on the other hand, is the procedure through which a centrifugation device or membrane-based replacement equipment removes a portion of blood plasma, and separates specific macro-molecules from the patient´s blood for therapeutic purposes.

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Received 27 June 2020; **Accepted** 20 July 2020; **Published** 27 July 2020

The removed substances include alloantibodies, autoantibodies, immunocomplexes, cytokines, exogenous toxins, monoclonal proteins, lipoproteins and excessively produced plasma components. The clinical benefit of therapeutic plasmapheresis is the elimination of pathological substances or the replacement of abnormal plasma components. Another benefit of plasmapheresis is its effect on immunomodulation. The American Apheresis Society (ASFA) reviews its clinical indications. It is a well-known procedure in ICUs and in clinics of various medical specialties today around the world. It is relatively safe, and its complications are usually minor [1-3].

Mechanism of action

The purpose of therapeutic plasmapheresis is to decrease the amount of immunocomplexes and other large molecular components that are found in plasma and that have a pathological inflammatory effect. After removing a certain volume of plasma, it can be replaced by donor plasma or by either a colloid or crystalloid solution.

Plasmapheresis procedures require the application of different technical aspects. Among them, anticoagulation should be mentioned, given its role in the prevention of thrombus formation in the extracorporeal device. Citrate (in centrifugal plasmapheresis) and unfractionated heparin (in membrane plasmapheresis) are commonly used.

The preferred venous access sites are the peripheral veins of the arms. However, another option is a central venous access in patients who will require longer treatments. In patients with chronic illnesses that require constant

plasmapheresis sessions, a special type of access, an arteriovenous fistula, can be created.

The following are the expected clinical effects of plasmapheresis [2,4]: (Table 1).

The methods of therapeutic plasma exchange can be divided into centrifugal and membrane filtration.

- **Centrifugal Therapeutic Plasma Exchange (cTPE):** Centrifugation systems divide plasma into its various compounds according to their different densities and molecular weight. Being the oldest method, it is the one that blood banks use. The downside is the increased risk of thrombocytopenia.
- **Membrane Therapeutic Plasma Exchange (mTPE):** It is carried out through the use of membranes that allow the filtration of substances such as immunoglobulins, immune-complexes, lipoproteins, complement factors and exogenous toxins. It is less effective for high molecular weight proteins such as IgM. Technically, it is a simple technique, with no risk of thrombocytopenia, but with an additional risk of hemolysis when done at high pressures [2].

Therapeutic indications

Plasmapheresis has been used to treat diverse pathologies, especially in the fields of neurology, hematology, dermatology, nephrology and rheumatology, although the amount of evidence for its use varies for each specific pathology. The American Society for Apheresis (ASFA) periodically reviews the indications for plasmapheresis. Current evidence supports its use for the treatment of 84 diseases with 157 different medical indications. Such indications are divided into four different categories [1,5,6]. (Table 2).

The most important pathologies in intensive care units that may require plasmapheresis are thrombotic microangiopathies, hyper-viscosity syndromes, Guillain-Barré syndrome, disseminated encephalomyelitis, myasthenia gravis, rapidly progressive glomerulonephritis, anti–glomerular basement membrane antibody disease, cryoglobulinemia, and post-kidney transplant reactions [1,5].

In addition, there are several plasmapheresis devices that can eliminate endotoxins and that can be used as an adjuvant treatment for critical situations such as septic shock [5,7].

There are some questions left to be answered. What other pathologies could benefit from therapeutic plasmapheresis? Which serum markers are the most specific and sensitive to use before and after the procedure, to quantify the clinical benefit for a specific pathology? What specific protocols of pharmacological treatment can be implemented along with plasmapheresis [8]?

Complications

The complications for therapeutic plasmapheresis can be diverse, but specific to the mechanism selected, whether it is cTPE with an increased risk of thrombocytopenia or mTPE with an increased risk of hemolysis. The most prevalent side effects are pruritus and paresthesia which present in about 0.7-12% of plasmapheresis sessions. Other significant side effects are hypotension, nausea, and the ones related to the vascular access such as bleeding and infection, or in the case of central venous accesses, pneumothorax [1].

Nanomembrane-based therapeutic plasmapheresis

Even though most of the complications for plasmapheresis are insignificant, its high cost as well as its technical difficulties, led to the creation of innovating devices that allow for nanofiltration. Nanomembrane-based plasmapheresis is a method of blood purification that removes toxic and inflammatory blood components. Regions in Russia, Bulgaria, France and other European countries have successfully implemented this technology. It basically consists of a device that pumps and filtrates the patient´s blood through nanopores in a multi-membrane layout [8-11].

Mechanism of action

A pump operating under the principle of “systole-diastole” conducts extracorporeal circulation through the nanomembrane-based filter. The filter separates blood components through multiple overlapping nanomembranes to dispose of specific macromolecules. These membranes consist of a polymeric film with a thickness of 10-15 μm, made of polyethylene terephthalate or polycarbonate, with pores created by argon particles accelerated through a cyclotron. Nanopores sizes range from 30 to 50 nm and can remove molecules weighing less than 40 kDa. The multiple layers of nanomembranes are put together by a special technique and then they are positioned in sterile conditions inside a plastic container with a dimension of 10 × 10 cm. This assembly constitutes the filter of the device and it consists of two chambers [8,9,11].

The whole process starts with a single IV line, preferably on the patients arm. Blood drawn from the patient is reconstituted with a solution (either crystalloid or colloid solution) and an anticoagulant (ACD-A). The pump controls the extracorporeal circulation and conducts the blood through the nanomembrane filter. Once the blood fills the first chamber, it passes through the nanopores, and the filtration process starts. The blood passes to the plasma chamber, inside the filter, and there, the corpuscular elements are separated. This system improves the stability of the extracorporeal circulation, preventing hemolysis. The filtered plasma is deposited in a collection bag, while the reconstituted blood is returned to the patient by the same IV access where it all started (Figure 1).

Table 1. Clinical effects of plasmapheresis.

S. No	Clinical effects
1	Reduction in the amount of pathogenic immunoglobulin G and immunoglobulin M type autoantibodies
2	Reduction of immunocomplexes, cryoglobulins and lipoproteins
3	Plasma removal and its replacement with a crystalloid or colloid solution, or with donor plasma. The aim is to administer substances lacking in the patient's plasma and eliminate what has been excessively produced.
4	Reduction of cytokines and complement factors
5	Increased formation of lymphocyte clones
6	Elimination of exogenous toxins

Table 2. Categories for plasmapheresis indications.

Category	Descriptions
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established.
	Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Therapeutic indications

Nanomembrane-based therapeutic plasmapheresis has various indications that adhere to the latest ASFA recommendations for membrane plasmapheresis. However, its specific characteristics are indicative of many more applications in various areas of medicine. It is an elective therapy that can be used in acute stages of many illnesses allowing for a fast organic and functional recovery. It has also been used for the treatments of chronic pathologies.

Here are some of its applications:

- It can be used by doctors and paramedics in accidents to treat pathologies such as crush syndrome.
- Detoxification treatment in chronic and acute diseases, as an adjuvant alternative.
- Plasma collection in transfusion centers.

There are specific reports of its use in patients with multiple sclerosis, neuromyelitis optica, and even in a patient with Acute Respiratory Distress Syndrome (ARDS) in the chronic context of myasthenia gravis [8-11].

Advantages

For now, it is the only method that allows for a minimally invasive plasmapheresis through a single peripheral venous access. The preferred peripheral venous access is the ulnar vein, generally needing an 18 G needle in adults, minimizing trauma to the vein with each puncture. Any other vein can be used, preferably in the arm.

The total extracorporeal volume is only 70 mL depending on the specific device used and the selected configuration. This is possible thanks to the discontinuous flow achieved through the "systole-diastole" system of the pressure piston. This limits the risks for unstable patients with cardiovascular disease and allows its use in children and the elderly. In the case of children, they may have a higher risk of complications, so the process should be done under strict observation.

Anticoagulant is administered through a manual adjustment device, and it does not depend on variations in perfusion parameters.

The nanomembrane-based plasmapheresis device, the solutions to be used and the nanofilter, are all easily transported due to their small size and weight (compared to other devices used for membrane or centrifugal plasmapheresis). Thus, it is used in the outpatient setting as well as in hospitals and in intensive care units.

Another advantage is its relative lower production, maintenance and application cost [8]. (Table 3).

Potential use of therapeutic plasmapheresis during the COVID-19 pandemic

Therapeutic plasmapheresis is an effective adjuvant treatment of acute liver failure, peripheral vascular disease, Guillain-Barré syndrome, sepsis, Disseminated Intravascular Coagulation (DIC) and Thrombotic Thrombocytopenic Purpura (TTP) which are all possible complications of Coronavirus Disease 2019 (COVID-19) [5,12,13]. (Table 4).

The following are published studies on the specific use of therapeutic plasmapheresis as an adjuvant treatment for COVID-19. In China, in 3 patients, after treatment with plasmapheresis the C-Reactive Protein (CRP) and IL-6 levels were significantly decreased and the lymphocyte and prothrombin time were improved [14]. In a retrospective, observational study (still under revision) adult patients with septic shock and multiple organ failure secondary to COVID-19 pneumonia, who received adjunct plasmapheresis showed improvement. Their hemodynamics and organ dysfunction did improve with plasmapheresis regardless of sepsis source [15]. In another study, three critically ill patients with COVID-19 in Wuhan, China, featured with profound inflammation and treated with plasmapheresis, showed an effect in managing cytokine storm and pathogenic antibodies [16]. Also, a series of 6 cases on

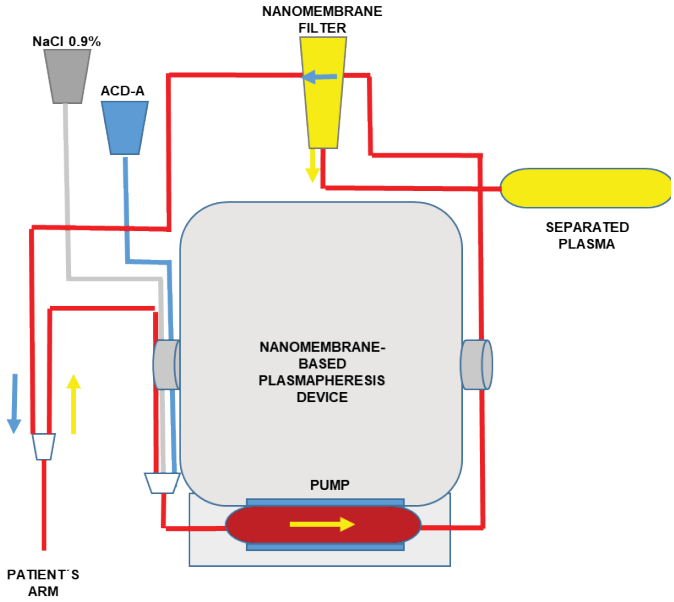

Figure 1. Nanomembrane-based plasmapheresis device.

Table 3. Characteristics of the nanomembrane-based plasmapheresis equipment (Adapted and translated from Gaspare, 2014).

S. No	Characteristics
1	Stable filtration process, thanks to the rigid protective filter coating
2	Reduction of trauma to erythrocytes and other plasma elements
3	Fulfills the requirements of the European Pharmacopoeia Commission and the Committee for Public Health of the European Council
4	Reduced priming volume
5	Reduced amount of plasma removed
6	Lower infectious and allergenic risk
7	Filling volume less than 20 mL
8	Weight of the filter: 100 mg
9	Dimensions of the filter: 85x85x35 mm
10	Plasma reception speed of up to 600 ml / hour
11	Sterile, flame retardant and non-toxic device
12	Autonomy and independence of electrical energy sources
13	Insignificant logistical requirements for transport
14	Fast operation

the effect of plasmapharesis in COVID-19–related autoimmune encephalitis, showed improvement soon after the initiation of the treatment, except for one patient [17].

SARS-CoV-2 has a diameter of 60-140 nm; large enough to be eliminated with some types of plasmapheresis (including nanomembrane-based therapeutic plasmapheresis). "This is the main rationale for performing plasmapheresis for critical patients with severe lung injury unresponsive to adjunctive treatments. It shows success in cytokine clearance. It can be considered as a salvage or adjunctive treatment with the rationale of clearing out the related cytokine storm and possibly viral burden" [18].

There are yet no articles on the specific use of nanomembrane-based plasmapheresis as a treatment for COVID-19. Also, therapeutic apheresis is not considered as a treatment option in Acute Respiratory Distress Syndrome (ARDS) in any of the existing management guidelines for any of the different plasmapheresis methods. However, a recent case report showed how nanomembrane-based therapeutic plasmapheresis used after non-invasive ventilation failure, helped a patient with ARDS and myasthenia gravis [11]. To explain this effect one thing to note is that many inflammatory mediators are involved in ARDS pathophysiology. It is characterized by disseminated inflammation of the lungs, causing severe hypoxemia. Many are the mediators that have been associated with such a syndrome, and almost all are small enough to be filtered through nanofiltration. Could this be the pathway in which

Table 4. Evidence for plasmapheresis use on COVID-19 complications.

Pathology/ Complication	Level of Rationale for therapeutic plasmapheresis Evidence		Duration and discontinuation/ number of procedures
Acute Liver Failure	Category I Grade 1A	Removal of albumin bound toxins as well as unbound toxins, and of inflammatory mediators	Daily until recovery
Peripheral Vascular Disease (Risk factor for severe COVID-19)	Category II Grade 1B for lipoprotein apheresis	Reduction of LDL cholesterol, the oxidized LDL, C-reactive protein (CRP), and fibrinogen transiently	10 sessions in less than 8 weeks. 1-2 sessions per week.
Guillain-Barré Syndrome	Category I Grade 1A	Reduction in pathological antibodies. It can accelerate motor recovery, decrease time on the ventilator.	5-6 sessions over 10-14 days
Sepsis	Category III Grade 2B	Removal of inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins and ADAMTS13.	Daily until recovery
DIC		Removal of tissue factor and plasminogen activator inhibitors-type-I, and replacement of antithrombin III, protein C, and coagulation factors	
Thrombotic Thrombocytopenic Purpura	Category I Recommendation 1A	Removal of the large and ultra-large VWF (von Willebrand Factor), removal of the ADAMTS-13 inhibitors and proteolytic inactivators, and replenishment of ADAMTS-13	Daily for 2-3 days until recovery

nanomembrane-based therapeutic plasmapheresis could be used for the treatment of the severe acute respiratory syndrome caused by COVID-19? [19,20].

Discussion and Conclusion

Many are the potential uses for plasmapheresis. However, there are some limitations given that not many high quality trials have been implemented. The ASFA has created the best source of evidence for the use of plasmapheresis and it supports its use for many types of chronic illnesses, such as autoimmune and neurological disorders. It also shows a high grade of evidence for the use of plasmapheresis on some of COVID-19´s potential complications, but its clinical relevance is left to be fully demonstrated. There are already a few published studies where plasmapheresis has been considered as an adjuvant treatment for COVID-19, but there is more to the general picture of how it could be used. The slow but steady extension of the use of plasmapheresis led to the creation of an innovative apparatus such as the nanomembrane filter and the nanomembrane-based plasmapheresis device. This apparatus has several advantages over other plasmapheresis methods. It is simple and has low production, maintenance and application cost. And it appears to be just as effective as other types of membrane plasmapheresis, with less risk of hemolysis. That´s the main reason why in the future nanomembrane-based therapeutic plasmapheresis should be given priority over other plasmapheresis methods in the implementation of high quality trials to confirm its use for some of the complications of coronavirus disease (COVID-19). It could be used during the most critical hours of the disease, for the control of the cytokine storm and the inflammatory state, given its proven effect by filtration of inflammatory mediators and other large molecules, which could end on a reduction of the viral load itself.

Conflict of Interest

Hereby we declare no conflict of interest.

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How to cite this article: Diego R Delgado and Ernesto Romero. "A Comparative Analysis between Nanomembrane-Based Therapeutic Plasmapheresis and Other Plasmapheresis Methods and Their Potential Use during the COVID-19 Pandemic" *Altern Integ Med* 9 (2020): 298 doi: 10.37421/aim.2020.9.298.