Review article

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Aquapheresis: Does it work?

Utilidad de la terapia de acuaféresis

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Abstract

The therapy of Aquapheresis has been studied as a therapeutic tool for patients with volume overload refractory to treatment with loop diuretics, whose main objective is to mitigate the clinical impact therein in patients with decompensated heart failure and cardiorenal syndrome, recognizing positive cumulative balances in critically ill patients as an independent factor for mortality. A search was made in the main scientific databases for review articles, and studies that included the Acuapheresis strategy. Bibliographic references were found in databases from 2005 to 2017. Aquapheresis therapy is a patented ultrafiltration therapy aimed at improving refractory overload in patients with congestive heart failure. There are gaps in knowledge regarding cost-effectiveness therapy, serious adverse events attributable to it and candidates who will benefit, and we believe that more quality studies are required to reach solid conclusions. So far there is no compelling evidence to support aquapheresis therapy to implement its routine use in the ICU.
Key words: Ultrafiltration, heart failure, fluid overload, cardiorenal syndrome, acute kidney injury, dialysis, extracorporeal, critical care.

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Resumen

La terapia de acuaféresis ha sido estudiada como una herramienta terapéutica para pacientes con sobrecarga de volumen refractaria al tratamiento con diuréticos de asa. Su objetivo principal es mitigar el impacto clínico de esta sobrecarga en los pacientes con insuficiencia cardiaca descompensada y SCR, reconociendo de esta manera los balances acumulados positivos en los pacientes críticamente enfermos como un factor independiente de mortalidad. Se realizó una búsqueda en las principales bases de datos científicas sobre la terapia de acuaféresis. Se incluyeron guías de manejo, ensayos clínicos controlados, revisiones sistemáticas y metaanálisis. Las bases bibliográficas que arrojaron resultados relevantes fueron Web of Sciences, Scopus, PubMed y SciELO y en total se encontraron 47 referencias bibliográficas publicadas entre 2005 y 2017. La acuaféresis es una terapia de ultrafiltración patentada que mejora la sobrecarga refractaria en pacientes con insuficiencia cardiaca congestiva. Hay brechas en el conocimiento en relación a su costo-efectividad, a los eventos adversos graves que se le atribuyen y a los candidatos que beneficia, por tanto, se requieren más estudios de calidad para llegar a conclusiones sólidas. Hasta el momento no hay evidencia contundente que respalde el uso sistemático y rutinario de la terapia de acuaféresis en las unidades de cuidado intensivo.
Palabras clave: ultrafiltración, falla cardiaca, sobrecarga fluidos, síndrome cardiorrenal, injuria renal aguda, diálisis, terapia extracorpórea, cuidado crítico.

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Introduction

Aquapheresis is an ultrafiltration (UF) therapy designed to eliminate fluid overload. In patients with congestive heart failure and cardiorenal syndrome (CRS) it has been studied as a therapeutic strategy to restore balance; achieve euvolemia in a safe, effective, and predictable manner, and reduce hospital stay and readmissions for acute decompensation and mortality. Likewise, it has been compared with conventional pharmacological measures, mainly with loop diuretics, to determine its efficacy in these aspects.

A compilation of the currently available medical literature is performed in this article in order to analyze the benefits and limitations of aquapheresis therapy.

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Materials and methods

A search was conducted in the main scientific databases on aquapheresis therapy. Management guidelines, controlled clinical trials, systematic reviews and meta-analyses were included. All the articles in which UF strategies for the management of fluid overload were mentioned and those that implemented aquapheresis therapy in adult patients were included. Articles related to the pediatric and obstetric population were excluded.

Results

The bibliographic databases that yielded relevant results were Web of Sciences, Scopus, PubMed and SciELO, and a total of 47 bibliographic references published between 2005 and 2017 were found.

Epidemiology

The incidence of acute kidney injury (AKI) depends on the definition used; however, this is a condition that can reach rates of 44% in hospitalized patients[1] and that in intensive care units (ICUs) can rise to 60%, being septic shock (50%) and sepsis (20%) the main causes.

About 6% of patients with sepsis who develop ARF require some type of renal support therapy, which constitutes an event with a high risk of morbidity and mortality and poor results in the short and long term.[2,3] Likewise, it is estimated that the mortality rates associated with ARF in patients with septic shock who undergo dialysis therapy ascend to 80%.[4]

On the other hand, more than 1 million hospitalizations per year for congestive heart failure (CHF) are recorded in the United States,[5] finding that 82% of patients hospitalized for this cause have some degree of kidney dysfunction in the first 48 hours after admission, which demonstrates that there is a complex crossover dialogue between the two organs.[6,7]

Cardiorenal syndrome

The term "cardiorenal syndrome" was proposed in the 1940s to describe the bidirectional interactions between the heart and the kidney,[8] it is defined as a state of advanced deregulation between these two organs and is mediated by compensation mechanisms that become insufficient and deleterious and generate systemic repercussions.[9]

In 2008, the Acute Dialysis Quality Initiative Group held a conference to define the CRS; in which this pathology was classified into five types according to the time and the primary organ affected[10]: type 1, acute CRS; type 2, chronic CRS; type 3, acute renocardiac syndrome; type 4, chronic renocardiac syndrome, and type 5, secondary CRS. Some examples of the latter are diabetes *mellitus* and sepsis, which simultaneously produce heart and kidney dysfunction. As a demonstration of the significant interaction between the heart and the kidneys, the dysfunction or injury of one organ often contributes to the dysfunction or injury of the other.[11]

Pathophysiology of CRS

From the pathophysiological point of view, CRS is the product of the connection of complex pathways, although the conventional explanation for its development in the context of a primary cardiocentric movement focuses on the inability of the defective heart to maintain an adequate cardiac output, which results in pre-renal hypoperfusion.[11] In this sense, the inadequate renal affeent flow activates the renin-angiotensin-aldosterone system (RAAS) and the autonomous nervous system through upregulation of the sympathetic system and secretion of arginine-vasopressin, leading to fluid retention and the subsequent increase in preload defined as the factor that has the greatest impact on the worsening of kidney function and heart pump.[12] In this context, the increased central venous pressure leads to renal venous hypertension and intrarenal blood flow insufficiency as well as increased renal resistance, which ostensibly affects the glomerular filtration rate.[12-14]

There are other mechanisms responsible for the development of CRS, for example, the activation of the neurohumoral axis increases sodium and water reabsorption in the proximal tubule, which maintains effective plasma volumes and eventually results in oliguria and makes congestion worse.[11]

There are two cardiovascular mechanisms that have a direct effect on the development and outcome of CRS and therefore affect renal hemodynamics: the right ventricular dysfunction (which generates a decrease in the preload of the left atrium and consequently of the left ventricle, with the subsequent drop in cardiac output) and interventricular asynchrony (which affects the cardiac cycle and the biventricular interaction). It is described in the literature that there are phenomena of biventricular interdependence (what happens in one ventricle consequently affects the other), but the tricompartmental model, which includes the heart, the pericardium and the interventricular septum is also proposed. In this way, the proper cardiac function will depend on the integrity of the interventricular septum, the intrapericardial changes and the transmural pressure of the heart. The alteration in these mechanisms greatly affects stroke volume, cardiac output, and renal hemodynamics.[15]

Among the non-hemodynamic pathways that aggravate the cardiac or kidney injury, chronic inflammation, the imbalance in the proportion of oxygen reactive species and/or production of nitric oxide and the persistent activation of the RAAS axis are fundamental for the activation of the sympathetic nervous system.[16] In experimental models, it has been found an elevation in the levels of tumor necrosis factor ? (TNF-?), interleukin-1 (IL-1) and interleukin-6 (IL-6) that has direct cardiodepressive effects, which result in a reduction of the left ventricle ejection fraction (LVEF). On the other hand, the so-called uremic nephropathy is characterized by the development of myocardial remodeling, with a significant burden of left ventricular hypertrophy, in which it has been demonstrated that the fibroblast growth factor-23 (FGF-23) has an independent causal effect.[17]

Since left ventricle hypertrophy is associated with a reduction in capillary density in the central endocardium, it is possible that microvascular ischemia plays a role in the progression of uremic cardiopathy. Meanwhile, peripheral venous congestion causes an endothelial tightening, which generates the conversion of the vascular endothelium of a proinflammatory phenotype into an inactive one and highlights the importance of decongestion in the natural history of the CRS, beyond its hemodynamic effects.[11]

Finally, they are data suggesting that dendritic cells play a role in the activation of adaptive immune responses in the context of the CRS. The reported data may represent a useful tool in future studies that allow to better understand the different mechanisms underlying the pathophysiological presentation of the syndrome and, in this way, develop alternatives to shorten the course of the chronic CRS.[18]

Impact of fluid overload

Fluid overload has been described as a factor of mortality in critically ill patients,[19-24] but it also has an important impact on the hospital readmissions of patients with congestive heart failure, since it has been estimated that about 90% of those who are admitted through the emergency department have signs and symptoms related to this overload and, once they are discharged, it is estimated that 25% are readmitted within the first 30 days and 50% within the first 60 days due to related symptomatology.[25]

Several studies have reported that volume overload is directly related to a lower probability of recovery of renal function, with a greater probability of the need to start renal support therapy, and the development of adverse events in almost all organs and systems. The study conducted by Shen *et al.*,[20] published in 2017 and derived from the analysis of a database of multiparameter intelligent monitoring in ICU, included 2,068 patients and found that the more negative the cumulative fluid balance and the lower the fluid intake were, the better the results were in terms of mortality with statistical significance, which is in consistent with the literature.

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Management of the overload

In order to mitigate the volume overload, diuretics have been considered the cornerstone of treatment in patients with heart failure; in the European guidelines to treat this condition their use is a recommendation in the management of this overload.[26] However, it has been found that such drugs have certain disadvantages in their routine use, since the changes in the intravascular volume they produce are unpredictable; likewise, it has been widely recognized that loop diuretics in the setting of ARF are related to a worsening of renal function associated with hypovolemia, which leads to an exponential increase in neurohormonal activation with the implications that this entails within the cycle.[11]

The use of high-dose diuretics is also related with hydroelectrolitic and acid-base imbalance, and with a reduced efficiency because about 40 % of patients may have diuretic resistance, defined as failure to achieve reduction of edema despite a full dose of loop diuretic (essentially 240 mg of furosemide or maximum dose of its equivalents), a fractional excretion of sodium (FeNa) <100 mmol/24 hours or an amount of excreted sodium as percentage of filtrate <0.2 %.[11]

The multiple causes of diuretic resistance include poor adherence to drug therapy, dietary restrictions, pharmacokinetic problems, and compensatory increases in sodium reabsorption in the nephron sites that are not blocked by the diuretic. [11] Felker *et al*.[27] report that patients who have already been chronically taking loop diuretics require doses 2.5-fold higher for the management of their acute condition.

Likewise, there is a series of direct and indirect pathophysiological events that explain this diuretic resistance and in relation to this risk, algorithms have been developed to mitigate it[28,29]; however, the high percentage of patients who do not respond to this therapy has raised the need to develop other therapeutic tools such as UF.

According to the guidelines for the management of heart failure, the UF can be considered for patients with refractory congestion who do not respond to diuretic treatments (IIB: *weak recommendation, moderate quality of evidence*) and renal replacement therapy should be considered for patients with refractory volume overload and acute renal failure (IIA: *weak recommendation, high-quality of evidence*).[26]

Considering the unmet need for the management of the overload, in a review of extracorporeal UF therapies, Constanzo *et al*.[30] include the studies that have used the aquapheresis therapy to improve the volume overload, and they state that, in contrast to diuretics, UF may be associated with more effective decongestion and fewer cardiovascular events; however, the essential aspects of UF are still poorly defined and it is clear that the adjustment of UF rates to the vital signs (systolic blood pressure) and the renal function of the patients is required.[30]

Ultrafiltration and aquapheresis

The principle that governs aquapheresis therapy is the convective transport, which explains that UF occurs in response to a transmembrane pressure gradient and depends directly on factors such as the permeability coefficient, the transmembrane pressure, the hydrostatic pressure of the blood, the ultrafiltrate and the oncotic pressure.[31] The convective principle governs the slow continuous ultrafiltration (SCUF) which shares technical characteristics with aquapheresis; the difference lies mainly in the pump flows and in the possibility of initiating aquapheresis therapy with a peripheral venous access, which suggests that it can be used in settings outside the ICU. There are some studies of SCUF in volume overload of CHF patients with disappointing results.[32]

Aquapheresis is an UF therapy designed to eliminate fluid overload with which balance is restored and euvolemia is achieved in a safe, effective and predictable manner. In a simplified approach of UF called the Aquadex Flexflow® System by its manufacturer, this therapy is approved by the Food and Drug Administration and is characterized by being a therapy that works with a

small, portable machine: it consists of a console that has friendly features for its programming and, although it requires trained personnel, it is relatively easy to use with a tentative programming time of less than 10 minutes. The amount and velocity of UF can be specified and adjusted in the programming console with pump flows (Qb) of 40 cc/min and gradual increments of 5 mL/min, which generates a gradual reduction of the overload with no significant clinical impact on hemodynamics or in the electrolyte balance.

Aquapheresis therapy has an important advantage that consists in that it can be connected to a peripheral venous access cannulating the basilic vein as the preferred route, followed by the external jugular vein or the antecubital vein; however, this generates reasonable doubt about the need of admission to the ICU and whether it would eventually have some interference on possible outcomes in relation to complications derived from the treatment in this unit. Aquapheresis can also be used by central line in the usual accesses.[33]

This system was designed to improve the symptoms and the clinical outcomes of the patients and can be implemented in temporary (up to 8 hours) or long term basis (> 8 hours) according to the degree of overload and the clinical indications, taking into account that the half-life of the filter is 24 hours.[33]

According to the manufacturer's characteristics, the volume of the extracorporeal circuit is 22 mL, the ultrafiltration range fluctuates between 0 and 500 mL/h, (increments of 10 mL/hour), with a priming volume of 50 mL and a reduced contact surface between the blood and the system, which ensures a minimal blood loss if the circuit coagulates and reduces the required doses of heparin. The standard dose of unfractionated heparin is 10-20 U/kg with monitoring guided by activated clotting time for targets of 180-220 seconds.[33]

During this therapy, the machine draws the blood of the patient and is directed to the system passing through a pump and a volume sensor, to reach later the hemofilter, which consists of a semipermeable membrane that allows the extraction of the plasma volume thanks to the hydrostatic pressure gradient; this generates the elimination of the isotonic fluid and subsequently the ultrafiltered blood returns to the patient.[30,33]

This machine also has a hematocrit sensor, which is optional, and is used to monitor and adjust the UF. On-line hematocrit sensors allow the continuous estimation of the changes in the blood volume during the UF and can be programmed to stop the fluid extraction if the hematocrit exceeds a threshold established by the physician (for example, 5% to 7%) and restart the therapy when the hematocrit value falls below the prespecified limit, which indicates an adequate filling of the intravascular volume from the interstitial space.

However, given that many factors such as changes in the position of the patient may alter the hematocrit values, physical, laboratory and hemodynamic variables should be assessed concomitantly to determine the appropriate UF rates and the amount of fluid to be removed.[30]

Objectives of fluid removal and monitoring of UF therapy

As a general recommendation, it is important that once the initial UF rate is chosen, to perform a clinical and, if possible, paraclinical monitoring and to make the pertinent adjustments in relation to slowing down the UF rate or stopping the therapy, given that the capillary filling of the interstitium decreases as the fluid is removed and it could have unfavorable outcomes in the hemodynamics of the patient.[34] Although the optimal rate and duration of UF must be individualized, UF rates >250 mL/h are not recommended in critically ill patients.[33]

Patients with predominantly right heart failure or with heart failure with preserved LVEF (>50 %) are more susceptible to intravascular volume depletion and they only can tolerate low UF rates (50-100 mL/h).[26] In addition, the clinical experience teaches that fluid removal with methods of

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extracorporeal dialysis is better tolerated when it is carried out with low UF rates and during prolonged periods.[33]

Indications for aquapheresis

The current indications for the use of aquapheresis therapy are volume overloads (defined as the presence of more than two peripheral edemas, ascites, pulmonary edema, jugular venous distention >7 cm or an increase by more than 5 kg), overloads that meet criteria for refractoriness to standard therapy (defined by the criteria of diuretic resistance) and patients with CRS and those in whom chronic renal failure has not been documented.

Aquapheresis therapy should be avoided in special conditions such as the need for renal replacement therapy for other causes in addition to overload, hemodynamic instability or hemoconcentration (Hematocrit > 53 %).[30,33]

It is worth mentioning that it is necessary to perform monitoring of the UF that includes clinical and paraclinical assessment of the response to therapy. Taking into account the low sensitivity and specificity of the physical examination in contrast with other techniques such as ultrasound or bioimpedance, joint assessment methods should be implemented, while recognizing that all the tools mentioned have evidenced limitations and are outside the scope of this review.[19,30]

Clinical evidence of aquapheresis

Although there is a record of previous pilot studies and case series, it was not until 2005 when the first articles that used the Aquadex 100® system were published; the last study was published in 2016:

The study conducted by Constanzo *et al.*,[34] published in 2005, included 20 patients and it result was in favor of UF (after receiving doses of diuretics) in relation to hospital readmissions for symptoms of CHF. In the same year, Bart *et al.*[35] published the RAPID-HF, a multicenter randomized clinical trial (RCT) conducted in 6 hospitals of the United States with a total of 40 patients diagnosed with CHF (defined as the presence or more than two edemas and one congestive symptom); in this research, the patients were randomly distributed into two groups of 20 subjects: in the first, the participants were assigned to the usual treatment, receiving a mean dose of 160 mg of furosemide with an outcome of removed volume of 2838 mL, and in the second, they were assigned to UF therapy and underwent a single session of 8 hours, receiving a mean dose of 80 mg of furosemide with a secondary outcome of total volume removed of 4650 mL. The primary outcome was the weight loss at 24-48 hours. In the results, a more marked volume removed was found in the patients who received UF, but in terms of the primary outcome, weight loss after 24 hours was 2.5 kg in those treated with UF and 1.86 kg in the groups treated with pharmacological therapy, without reaching statistical significance (p=0.240).

In 2007, Constanzo *et al.*[36] published an RCT conducted in 200 patients, that compared the safety and efficacy of UF versus loop diuretics using the Aquadex 100® system and where the mean elimination rate was 241 mL/h during 12 hours. The patients received diuretics intravenously during 24 hours, twice the daily oral dose they received before the hospitalization. The primary outcome was the weight loss and the improvement in the dyspnea assessment scale at 48 hours. The secondary outcomes were: net fluid loss at 48 hours, decline in functional capacity (assessed by 6-minute walk test, New York Heart Association functional class scale and Minnesota Living with Heart Failure scale at 30 and 90 days) and hospital readmissions for CHF at 90 days. It was also found that patients undergoing UF therapy had, on the one hand, fewer hospital readmissions as a result of volume overload and, on the other hand, an improvement in weight, but without significant changes in the dyspnea scale and with deterioration in kidney function.

By the year 2012, Bart *et al.*[37] published a study that again sought to evaluate the differences between UF therapy and diuretics in relation to the creatinine level and body weight at 96 hours; for this, a follow-up was carried out during 60 days. This was a

multicenter RCT that included 22 hospitals in the US and Canada, with an initial number of enrolled patients of 15,871, that is, up to that point it was the largest study regarding aquapheresis therapy in the clinical setting of management of fluid overload in patients with CHF. However, it only was possible to recruit 1.18 % of the sample (188 patients) due to the interruption futility and adverse events. The patients had a CRS, defined as CHF with two or more signs of congestion and acute kidney injury categorized as KDIGO I. It is necessary to mention that 77% of the participants had been hospitalized for CHF during the previous year and that in the baseline characteristics the patients in the UF group had lower LVEF and a higher level of N-terminal pro-brain natriuretic peptide (NTproBNP) than the group of pharmacological therapy with loop diuretics.

The patients treated with UF were programmed at a fixed rate of 200 mL/min/1.73 m^2 with a mean duration of 40 hours, which could be unfavorable for those who were more dependent on the preload to maintain the hemodynamic stability. Pharmacological therapy was staggered to obtain a target diuresis of 3 to 5 L/day, with a mean dose of furosemide of 120 mg/day and a mean duration of 92 hours.[37]

The results of Bart *et al*.[37] evidenced a significant increase in creatinine levels with the UF therapy in the first 7 days, but there was no significant difference in weight loss at 96 hours. In the light of the findings, only 10 % of the patients had an adequate improvement in the signs of fluid overload at 96 hours and 43 % of the patients died or were readmitted for CHF within the 60 days of study; in the same period the mortality was higher in the patients who underwent UF therapy (17 %) than in those treated with diuretics (14 %) (p=0.4651).

Among the adverse events of this study,[37] it is described that 72% of the patients in the UF group presented problems with the catheter, acute functional renal failure or gastrointestinal bleeding (p=0.033). However, the analysis of these results obliges to consider that 39 % of the patients received concomitantly diuretics, which affects the adjudication of the events to one or other therapy. The conclusions of the research indicate that in the UF therapy there were more costs and a worse renal function, furthermore, there were no significant changes in terms of improvement of the congestion.

In 2013, Wen *et al*.[38] published a systematic review that included 5 RCTs, with a total of 477 patients, and they found in the primary outcome a greater weight loss at 48 hours and a greater net volume removal in patients treated with UF therapy, although the first outcome presented a heterogeneity index (I^2) of 51 %. In this review, the adverse events did not show statistically significant differences.

One year later, Barkoudah *et al*.[39] published a meta-analysis which included 9 RCTs, with a total of 613 patients, and they found an advantage in favor of the UF in the outcome of the mean weight loss, with an I^2=66.8 % and without differences in the outcomes of changes in creatinine and mortality from all causes. The significant heterogeneity of this meta-analysis is due to the fact that within the studies assessed there were differences in the type of therapies; likewise, continuous veno-venous hemodiafiltration, intermittent hemodiafiltration and aquapheresis were included, and different machines were used, which makes it difficult the correct interpretation of the results.

Finally, in 2016, Constanzo *et al*.[40] published a multicentric RCT conducted in the United States, with an initial number of 810 patients with a diagnosis of CHF. The study was discontinued unilaterally and prematurely by the sponsor, which was justified by a slow recruitment when only 27.5% of the initial sample had been reached. However, 224 patients were randomized into two groups, one of 110 patients who were assigned to a UF session adjustable to renal function and systolic blood pressure, and another of 114 patients who were assigned to drug therapy. The primary outcome was the development of CHF symptoms within 90 days and cardiovascular events.

The mean UF rate in this study was 138 mL/h and it was administered during a longer period (70 hours). Among the secondary outcomes, it was found a trend towards a longer time until the presentation of the

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first event of heart failure within 90 days and less cardiovascular events in the UF group, which was attributed to the fact that the UF restored the patient's response to the diuretic agent as key mechanism to delay the recurrence of CHF events.[40]

However, it is not encouraging that the primary outcome did not present statistical significance due to the limitation of the incomplete statistical analysis of the data given the sample size, which was insufficient to reach a power of 90% with the Log-Rank test.

On the other hand, adverse events occurred in 31 % of UF patients, 14% being recognized as serious, which include cardiovascular disorders such as acute myocardial infarction, cardiac arrest and, paradoxically, increased heart failure and cardiogenic shock, in addition to the complications derived from the procedure. The analysis of mortality derived from one or the other therapy did not show a statistical difference and it was found that 70% of all the cases of death were due to cardiovascular causes.

In the literature, there are two more studies conducted in Italy: the ULTRADISCO,[41] which included 30 patients who received UF therapy with the PRISMA® machine and in which clinical, biohumoral and hemodynamic variables were evaluated at 36 hours, and it was found that the UF was associated with a greater reduction of body weight, improvement in the signs and symptoms of CHF, decrease in the aldosterone and NT-proBNP levels and systemic vascular resistance, which results in improvement in the objective cardiac output measurements; and the CUORE,[42] conducted in 56 patients with the Dedyca Device® machine and that reported in its primary outcome that patients under UF therapy had less hospital readmissions for heart failure in the 1-year follow up.

In terms of costs, which is a matter of current concern, there is a limited evidence: Bart *et al*.[37] concluded that the UF therapy was more expensive, and Constanzo *et al*.[43] published a study of cost analysis of UF versus diuretic therapy for patients with heart failure from the hospital perspective in which they reported a cost saving of USD$3,975 by reduction of readmissions at 90 days in the patients who received UF therapy.

Discussion

It has been suggested that there is a direct relationship between volume overload and mortality, hence the need to use therapeutic strategies that reduce this overload and improve the clinical outcomes of the patients by reducing the body weight (in terms of overload), the hospital readmission rates and the number of cardiovascular events.

Taking into account the principle of diuretic resistance, aquapheresis therapy has been presented as a tool that allows the removal of fluid and improves clinical outcomes, but requires to be individualized due to the risk of instability and complications associated with the procedure. Since the year 2004, studies comparing this therapy with conventional pharmacological management have been published in order to evaluate efficacy and safety. However, in the initial studies there are limitations derived mainly from the small samples and low follow-up, while in the large studies published later the limitations are due to premature discontinuation, either due to futility, adverse events or slow recruitment, which makes it very difficult to draw strong conclusions.

In this sense, so far there is no convincing evidence to support the systematic use of acuapheresis therapy in patients with volume overload. A possible explanation would be that it is not clear to which extent the clinically established overload of the patients corresponds to extravascular water, which translates into a lack of knowledge as to whether, despite the edema, the effective intravascular volume is contracted and would largely explain the failure of therapy.

Given the panorama, it is clear that there is a clinical challenge in the creation of diagnostic tools that allow the objective measurement of the volume status, as well as gaps in knowledge regarding the cost-effectiveness of therapy, the actual relationship

of serious adverse events attributed to it and the candidates who would benefit from the intervention. Therefore, the authors consider that more high-quality studies are required to reach solid conclusions.

Conclusions

There is a directly proportional relationship between the volume overload and mortality, being the diuretics the cornerstone of treatment to mitigate it. However, there are a non-negligible percentage of patients who present diuretic resistance of multifactorial etiology. Such resistance makes UF an attractive therapeutic tool; however it requires to be adjusted and individualized in order to improve the clinical impact in patients with refractory overload.

The clinical evidence yields promising results in relation to the tendency to reduce the body weight in terms of overload to lessen hospital readmission rates and the occurrence of cardiovascular events, with a subsequent decrease in total costs of care. However, both the initial studies and the large research published later have limitations in the analysis of results derived from premature discontinuation, either due to futility, adverse events or slow recruitment, which makes it very difficult to draw firm conclusions about the benefit of aquapheresis therapy as superior to pharmacological treatment with loop diuretics. The incomplete statistical analysis of the data due to insufficient sample size to reach a power of 90 % with the *Log-Rank* test allows to evaluate trends, but not to establish solid conclusions.

From the pathophysiological point of view, if the problem is overload, the question arises as to why aquapheresis therapy, despite reducing the weight by water extraction, has no relevant clinical impact on the outcomes. A reasonable analysis could be that it is not clear to what extent the clinically established overload in patients corresponds to extravascular water, resulting in a lack of knowledge as to whether, despite the edema, the effective intravascular volume is contracted; this would explain to a great extent the failure of the therapy. In this way, it is recognized that there is a clinical challenge in the creation of diagnostic tools that allow the objective measurement of the volume status.

On the other hand, there are gaps in the knowledge of the cost-effectiveness of aquapheresis therapy, the real relationship of serious adverse events attributable to it, and the candidates who would benefit from the intervention. In this sense, more high-quality studies are required to reach solid conclusions, since up to now there is no conclusive evidence to support the systematic and routine use of this therapy in the ICU. There is currently a study which is waiting the results on the topic of aquapheresis[44] and two studies in recruitment process,[46] which will surely make important contributions to the critical analysis of the evidence for this therapeutic tool.

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Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

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Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

Diana Ávila: Conception and design of the article, literature search, reading of articles, analysis and processing of information, writing and sending of the manuscript.

Andrés Bernal: Conception and design of the article, reading of the articles, analysis and processing of information, scientific and methodological advice on the design of the article and scientific terminology

Conception and design of the article, reading of articles, analysis and processing of information, scientific and methodological advice, editorial corrections

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