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Aquapheresis: An Institutional Experience

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ABSTRACT

Background: Aquapheresis (AQ) consists of the extracorporeal extraction of plasma water from the vascular space across a semipermeable membrane in response to a transmembrane pressure gradient. The primary utilization of AQ has been in the management of patients with diuretic resistant heart failure with a treatment goal directed to quickly eliminate the excess fluid and optimize volume status. This modality is similar to isolated ultrafiltration performed on those patients requiring dialysis, but utilizes a machine that is smaller and easier to initiate and operate compared with traditional dialysis equipment.

Method: A retrospective study that describes the indications in which AQ was utilized at Lenox Hill Hospital. The patient list was generated by searching for the keyword "Aquaph" in our electronic health record (EHR) orders. Patients were categorized based on hospital location and indication of AQ therapy. Additional information includes duration of treatment (days), changes in creatinine (start of AQ to stop of AQ), and total volume removed.

Results: The search generated 28 patients; five were excluded as AQ was not initiated. In the remaining 23 patients, the mean aquapheretic volume per day was 1954 mls, with no significant change in creatinine. Indications for AQ broke out into five main categories: cardiogenic shock including post cardiothoracic procedure (10 pts); anasarca (5 pts); ATN with volume overload (4 pts); ESKD with bridge ultrafiltration between hemodialysis treatments (2 pts); and post-op volume overload (2 pts).

Conclusion: We found that aquapheresis can be utilized in situations other than diuretic resistant heart failure. Also to consider, is the ease in which this less complicated aquapheresis equipment can be operated compared to the more complex hemodialysis equipment.

INTRODUCTION

Management of volume overload is an important component in the care of critically ill patients. Diuretic use is commonplace, and many critically ill patients need fluid removal with renal replacement therapy. Modern diuretics have been in clinical use for over 70 years [Eknoyan 1997]. Loop diuretics remain the cornerstone of treatment in these cases of volume expansion and edema, but have limitations and may be less effective with prolonged use. In addition, unfortunately, ECF volume expansion can persist, despite the use of multiple diuretics blocking sodium uptake throughout the nephron [Ter Maaten 2017]. With the limitations of diuretics in mind, it seems reasonable to consider novel therapies to optimize volume status. Ultrafiltration is the extracorporeal extraction of plasma water from the vascular space across a semipermeable membrane in response to a transmembrane pressure gradient [Ronco 2001]. This process removes fluid by convection whereas, hemodialysis provides both clearance and ultrafiltration via diffusion and convection, respectively. Isolated ultrafiltration, or slow continuous ultrafiltration (SCUF), are the terms applied when this technique is used in end stage kidney disease (ESKD) patients already on dialysis. In contrast, aquapheresis (AQ) refers to ultrafiltration in patients without ESKD [Jaski 2003]. Presently, aquapheresis has been almost exclusively initiated in patients in need of rapid treatment of volume overload, specifically those with decompensated congestive heart failure [Ronco 2001; Jaski 2003]. In fact, the primary indication for aquapheresis has been in the management of patients with diuretic resistant heart failure (ADHF) [Ronco 2001; Kazory 2018]. Although the utilization of aquapheresis has been studied in patients with ADHF, the potential of this therapy has not been fully explored in other patients who require fluid removal. Additionally, with the development of the more portable and user-friendly devices that are dedicated to isolated UF, patients can now readily receive aquapheresis therapy [Jaski 2003; Kazory 2018; Costanzo 2019].

This present report describes our experience with aquapheresis therapy at Lenox Hill Hospital and explores potential situations other than heart failure in which aquapheresis may be utilized.

METHODS

This is a retrospective study that describes the indications in which aquapheresis was utilized at Lenox Hill Hospital (LHH), a 350-bed, acute tertiary care hospital in New York City. Records of patients who received aquapheresis therapy

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Table 1. Number of patient and hospital unit

Location	Patient number
Cardiothoracic ICU	16
Coronary care unit	5
Medical ICU	1
Surgical ICU	1

over 18 months were reviewed. The patient list was generated by searching for the keyword "Aquaph" in the LHH Electronic Medical Record (EMR) orders. Patients were further categorized based on hospital location and indication for aquapheresis therapy. Additional information includes duration of treatment (days), changes in creatinine (start of AQ to stop of AQ), and total volume removed. All cases were being followed by the nephrology team, and the use of the AQ was at the discretion of the nephrologist overseeing the case. In most instances, the AQ was initiated after failed diuresis.

Aquapheresis equipment includes an Aquadex console (CHFSolutions, Minneapolis, Minnesota), an extracorporeal circuit that is comprised of a filter and tubing. Patients require a venous access to draw blood from the patient through the filter and a second venous line to complete the circuit, returning the blood to the patient. Two large bore peripheral intravenous lines are acceptable, though in this report all patients had a percutaneous dual lumen venous dialysis catheter. The extracorporeal circuit is 33 ml. The console has two pumps, one to control the extracorporeal blood flow rate through the circuit and the other to regulate the ultrafiltration. The blood flow rate can range from 10 ml/min to 40 ml/min (in contrast to continuous veno-venous hemodialysis or acute dialysis treatments that run 200 to 400 ml/min) and can generate an ultrafiltration rate up to 500 ml/hr.

RESULTS

The search generated 28 patients, of which five were excluded as they never actually received aquapheresis treatment. In the remaining 23 patients, a total of 98 AQ days were included. Average duration was 4.26 days per patient. The mean AQ volume per encounter was 8328 mls. The mean AQ volume per day was 1954 mls, with no significant change in creatinine.

Indications for aquapheresis broke out into five categories: cardiogenic shock including post-cardiothoracic procedure (10); anasarca (5); ATN with volume overload (4); ESKD with bridge ultrafiltration between hemodialysis treatments (2); and post-op volume overload (2). There were 16 patients from cardiothoracic ICU, five patients from CCU, one patient from medical ICU, and one patient from the surgical ICU (Tables 1 and 2).

In the two patients with ESKD on hemodialysis, acute changes in respiratory status at night triggered the use of AQ. Both patients had dialysis catheters for access and were in

Table 2. Five major indications for which aquapheresis was utilized

Indication	Patient number
Cardiogenic shock including post-cardiothoracic procedure	10
Severe anasarca without cardiorenal syndrome	5
ATN with volume overload	4
Bridge ultrafiltration in ESRD patient	2
Post-op volume overload	2

critical care areas facilitating the procedure. The critical care nurses handled the therapy obviating the need to notify the hemodialysis nurse on call. Of the cardiothoracic cases, two patients underwent AQ within two days of surgery to quickly remove more fluid than the diuretics yielded. Another case had a suboptimal response to bumex drip. The cases with anasarca were showing electrolyte perturbations that restricted ongoing diuresis. The AQ was successful in removing additional fluid, generating a net negative fluid balance for the days in use.

Overall, in this critically ill population, seven patients expired.

There was no difference in creatinine levels before and after AQ therapy. Each subject was able to complete the AQ prescription, in that goal UF was obtained as specified. Since this present report was not a controlled trial, it is difficult to compare outcomes with other patients who did not undergo this therapy. In addition, the cases selected are not comparable to prior reports describing the use of AQ in traditional CHF patients. Clearly, randomized controlled trials are needed in this arena.

DISCUSSION

ECF volume expansion has been an affliction for as long as medicine has been recording human pathology [Eknoyan 1997]. The term "dropsy" is readily found in the medical literature in the early nineteenth century describing edematous individuals. The introduction of loop diuretics in the 1960s, was a pivotal medical breakthrough for the treatment of these conditions [Stason 1966]. However, finding the optimal dosage for an individual takes time and can be a trial and error scenario. A variable response to diuretics is well known. Loop diuretics require a threshold plasma concentration, then have a steep dose-response curve until a ceiling is reached. Unfortunately, it is not always easy to determine the correct threshold dosage in a given individual, particularly when confronting renal and/or cardiac co-morbidities. Another limitation attenuating effectiveness is post-diuretic sodium retention, from an increase in tubular avidity for sodium once the diuretic has been cleared. Adding to this complexity is the concern over bioavailability, gastrointestinal absorption rates, and renal handling of loop diuretics [Ellison 2019; Costanzo 2007].

Table 3. Summary of three studies regarding use of aquapheresis versus diuretics

Year published	Study	Result	Summary
2007	UNLOAD	Favors UF	UF was found to safely produce greater weight and fluid loss at 48 hrs and also 53% reduction in 90-day risk of rehospitalization
2012	CARESS-HF	Favors Diuretics	Aquapheresis was not helpful due to worsening of renal function, and persistent congestion
2016	AVOID	Favors UF	Supported use of aquapheresis to lower rehospitalization rates in heart failure patients

In this regard, a shift from diuretics, which can result in an unpredictable rate of fluid removal, to an automated decongestive method seem practical, though future investigations will be needed to guide us. In theory, this latter approach yields more predictable and immediate fluid removal and avoids over-diuresis, intravascular volume depletion, and subsequent drop in renal perfusion.

There are three major trials that have examined the effectiveness of aquapheresis in the management of acute decompensated heart failure compared with diuretics (Table 3). The Ultrafiltration Versus Intravenous Diuretics for Patients hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, published in 2007, compared efficacy of ultrafiltration vs. fixed dose intravenous diuretic therapy in hypervolemic heart failure in 200 subjects randomized to either ultrafiltration or intravenous diuretics groups. The authors found that ultrafiltration safely produced greater weight loss and fluid loss at 48 hours, improved dyspnea score, and showed a 53% reduction in the 90-day risk of rehospitalization for heart failure, compared with intravenous diuretics. There was no significant difference in serum creatinine between the two groups [Costanzo 2007].

The 2012 Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial addressed the role of ultrafiltration in acute decompensated heart failure complicated by cardiorenal syndrome. The investigators randomized 188 acute heart failure patients with increased serum creatinine to either UF with a fixed regimen fluid of removal or dose adjusted diuretic therapy. At 96 hours, there was a significant increase in serum creatinine and adverse events in the UF group, but no difference in weight change and outcome between the UF and diuretic groups [Bart 2012; Bart 2012]. However, one major limitation of the CARRESS-HF trial is that UF was stopped prematurely in most patients in the UF group, whereas most patients remained on treatment in the diuretic group [Grodin 2018].

The Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial in 2014 was a multicenter randomized study to evaluate the efficacy of aquapheresis vs. IV diuretic in 810 hospitalized heart failure patients [Agostoni 1994]. The trial prematurely was terminated, due to slow enrollment after enlisting only 224 patients (27.5%). The primary endpoint of "days to first heart failure event after hospital discharge" showed no difference between groups. There also were no differences in the secondary end points of 90-day mortality, length of stay, or change in renal function. Of note, UF was associated with significantly greater total fluid removal (18.7 versus 14 liters, $P = .015$) and net fluid loss (12.9 versus 8.9 liters, $P = .006$) [Costanzo 2016]. These latter findings set the stage for further investigation into the utilization of this modality for removal of fluid for those patients not responsive to other maneuvers.

The concept to mechanically remove fluid from individuals with ECF volume overload is certainly not new as ultrafiltration is one of the major objectives of dialysis therapy. Dividing individuals with volume overload into only two groups, dialysis dependent or non-dialysis, ignores the continuum of ECF volume disorders, which many individuals experience and clinicians struggle with on a daily basis, while trying to generate a negative fluid balance. We need to broaden the approach when diuretics fail. Aquapheresis offers the convenience of pure ultrafiltration. Venous access easily is obtained with two peripheral intravenous lines, though in all of our cases, we placed temporary dialysis lines. A recent review by Costanzo describes details and limitations of the trials utilizing AQ in acute heart failure patients. The author offers insights as to what future studies need to examine, emphasizing individualized aquapheresis therapy adjusted by patients' haemodynamic and renal profiles. Guided objectives, in terms of total volume of fluid removal, duration of UF and UF rate, need to be established and utilized for better clinical outcomes [Costanzo 2019].

A recent report describes an innovative use of AQ improving clinical outcome. The study found that the prevention of fluid overload by the use of AQ in children with cardiopulmonary failure requiring extracorporeal membrane oxygenation (ECMO) improved survival in the ICU. This article describes the use of AQ in tandem with ECMO especially in cases of anuric AKI to provide UF with minimal hemodynamic disturbance [Constantinescu 2019]. Unlike diuretics, controlled ultrafiltration has the theoretical advantage of being able to adjust UF rates as frequently as needed to optimize net fluid removal while not exceeding capillary refill rates in real time. For example, it is known that individuals with right-sided heart failure or heart failure with preserved EF are sensitive to fluid removal and react in a "intravascular volume depleted manner" when diuresed. Subsequent activation of the neurohormonal system will further reduce effective diuresis. It has been demonstrated that efficient correction of the volume expanded state occurs with low constant rates of diuresis or UF over an extended period of time. In this manner, AQ facilitates the "siphoning" of extravascular fluid, while maintaining renal perfusion, thereby keeping the neurohormonal system quiescent. In addition, since ultrafiltrate is isotonic to plasma, more sodium per liter can be removed with UF

than with diuretic agents [Agostoni 1994]. The device has the advantage of a small size, low blood flow rates, low extracorporeal blood volume (33 ml), and the flexibility to adjust UF rates between 0 – 500 ml/hour [Costanzo 2020]. The device also is user-friendly to critical care nurses taking 15 minutes or less to initiate therapy.

In conclusion, our study demonstrates an expanded inpatient use of AQ beyond CHF patients. It is an adjunct therapy when isolated UF is needed in various clinical settings, including anasarca, ESKD, and delayed response to diuretics. Randomized controlled trials are needed to further explore the use of this modality, which is better suited to the nephrologist or critical care physician rather than the cardiologist as has been seen in prior publications.

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