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Can Ultrafiltration be Used as Primary Treatment of Congestive Heart Failure?

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Abstract

Objective: To determine whether ultrafiltration can be used as primary treatment of Congestive Heart Failure.

Study Design: Review of three English language, non-blinded randomized controlled trials from 2005, 2007 and 2008.

Data Sources: Randomized, controlled, non-blinded clinical trials comparing ultrafiltration to intravenous diuretics found using Ovid Medline and PubMed databases.

Outcome measured: Weight loss after 48 hours was measured at discharge, and at days 10, 30, and 90 post-discharge. Dyspnea after 48 hours was measured as a perception of the patient on a scale from 1 to 7, 1 being markedly worse, 7 being marked improvement. Net fluid loss after 48 hours was measured as ultrafiltrated in the ultrafiltration group and as urine output in the intravenous diuretic and usual care groups. Finally, rehospitalizations for heart failure-related issues was measured, starting on the day of discharge through 90 days post-discharge.

Results: There were statistically significant results for weight loss during hospitalization, and the p-value for rehospitalization for symptoms of heart failure 90 days post-treatment was < 0.05. Net fluid loss over 48 hours was didn't prove to be significant. Hypotension was the most frequent adverse event reported, but was not reported consistently throughout all three studies; one study didn't report adverse events at all.

Conclusions: The studies have proven ultrafiltration to be a safe alternative to intravenous diuretics for the treatment of congestive heart failure but there is not enough consistent, significant data to say that it can be used as initial primary treatment. Further studies with larger and more specific sample populations need to be done in order to better prove true long-term efficacy and cost-effectiveness.

Key Words: Ultrafiltration, CHF, Heart Failure

Introduction:

Congestive Heart Failure is a growing health concern for the aging and elderly population in the United States. Heart Failure is the mechanical failure of the heart and occurs when it is no longer able to pump blood at an output sufficient enough to meet the metabolic demands of the entire body.[1] It should be noted that there are many different subtypes of heart failure but the common thread is the profound decrease in cardiac output. More specifically, ventricular remodeling and neurohormonal activation of the sympathetic nervous system as well as the renin-angiotensin-aldosterone system are enormous players in the pathophysiology of heart failure.[1] This pathophysiology leaves the patient with symptoms of fatigue, orthopnea, a chronic non-productive cough, peripheral edema, and dyspnea on exertion or at rest, depending on severity. All symptoms are the result of hypervolemia; an environment primarily created by the neurohormones from the kidneys that increase retention of water and sodium.[1] Fluid regulation, therefore, is the primary target of heart failure treatment.[1] This paper focuses on three randomized controlled trials (RCTs) that evaluated the overall efficacy of ultrafiltration as primary treatment for congestive heart failure and its ability to decrease recidivism as well as cost by decreasing hospital stay.

Congestive heart failure is of major relevance to the Physician Assistant practice because it is a wide and growing diagnosis. 5.8 million people in the U.S. have heart failure with approximately 10 per 1000 people being diagnosed after 65 years of age.[2] 1 in 5 patients die within the first year of diagnosis.[2] Ultrafiltration has the potential to offer patients decreased hospital stays, less recidivism, and longer lifespan.[2] Heart failure is the leading cause of hospitalization in patients > 65 years of age and 65% are re-hospitalized

in a one-year period. In addition, the most common causes of heart failure are three of the most common disease processes that Physician Assistants in any field of medicine may encounter in their careers: Coronary Artery Disease, Hypertension and Diabetes. In 2010, heart failure was estimated to cost $39.2 billion.[2] The estimated 3.4 outpatient visits per heart failure patient per year contribute to the extensive cost.[2]

Approximately 90% of the annual hospitalizations for heart failure are the result of patients suffering the symptoms of volume overload.[3] Current treatment recommendations are aimed towards achieving euvolemia, most commonly treated with intravenous diuretics.[3] More and more hospitals, however, are trying ultrafiltration due to the prevalence of diuretic resistance and post-diuretic sodium retention. Post-diuretic sodium retention results in inadequate diuresis and the return of hypervolemia symptoms.[3]

An overwhelming 88% of patients are treated with intravenous diuretics and sodium restriction from diet.[4] While intravenous diuretics can be effective for congestive heart failure, ultrafiltration is being proposed as primary treatment here because fluid removal by this process can improve cardiac output and renal perfusion without altering glomerular filtration rate, NaCl uptake in the kidneys or renin secretion as intravenous diuretics tend to do.[3] Ultrafiltration is also being proposed as primary treatment because heart failure patients may require less hospitalization time over the course of their disease.

Objective:

The objective of this review is to determine if ultrafiltration can, in fact, be an effective alternative as primary treatment for congestive heart failure patients. Previously

studied randomized controlled trials have suggested that ultrafiltration can produce greater fluid loss and maintain this fluid loss at 90 days from the time of treatment, thereby decreasing recidivism.[5]

Methods:

All three randomized controlled trials utilized for this review were selected because their population group included hospitalized heart failure patients greater than 18 years of age. The interventions used for these heart failure patients was ultrafiltration and the comparison group was heart failure patients treated with intravenous loop diuretics such as 20mg Furosemide, 10mg Torsemide, and 1mg Bumetanide.

Information obtained for this review was found using both Ovid Medline and PubMed databases. Inclusion criteria included randomized controlled trials limited to the English language and published data. The keywords used were "Heart Failure", "CHF", and "Ultrafiltration". Further inclusion criteria was based on relevance and whether or not the outcomes evaluated in the studies dealt with POEMS (patient oriented evidence that matters). Exclusion criteria included DOEMs (disease oriented evidence that matters) and studies that were not previously used in any systematic review or meta-analysis found on the Cochrane Database. Studies were not excluded based on lack of statistical significance. Ultimately, three studies were found and analyzed and they included: 1) a randomized, non-blinded, multicenter controlled trial comparing ultrafiltration to intravenous diuretics in patients hospitalized with heart failure, 2) a randomized, non-blinded controlled trial comparing the renal effects of ultrafiltration to those of intravenous furosemide, and 3) a randomized, non-blinded controlled trial

comparing ultrafiltration to "usual care" consisting of intravenous furosemide and intravenous inotropes.

Outcomes measured in all three trials dealt with patient oriented evidence that mattered to the patients. For example, in all three studies, weight loss was measured after 48 hours, at discharge, and at 10, 30 and 90 days post-discharge for both the ultrafiltration and the intravenous diuretic groups. Dyspnea was also noted after 48 hours and measured as a perception of the patient on a scale from 1 to 7; 1 being markedly worse.[5] In addition, a 6-minute walk distance was performed to also measure dyspnea. The ultrafiltrate removed was measured right at the patient's bedside. This value was recorded as net fluid loss after 48 hours. For the intravenous diuretic and usual care groups, this value was recorded as urine output. The final outcome measured that mattered to patients was the number of re-hospitalizations within a 90-day period for heart failure related issues.[5]

Results:

Major demographics and characteristics of the studies utilized for this review are displayed in **Table 1.** It can be noted that all three studies had very similar inclusion criteria, including: ≥2+ pitting lower extremity edema, jugular venous distention, ascites, pulmonary edema or pleural effusion, and ≥ 2-pillow orthopnea. All patients were older than 18 and being hospitalized for congestive heart failure at the time of the study.

Table 1 – Demographics & Characteristics of included studies:

Characteristics of studies included in Systematic Review of the effectiveness of Ultrafiltration as primary treatment for Congestive Heart Failure.							
Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bart et al., 2005	RCT	40	> 18	2+ edema of LE at least one of the following: elevated JVD, pulm edema, pleural effusion, ascites	Severe stenotic valvular disease, ACS, Systolic BP < 90mmHg, HCT > 40%, poor peripheral venous acces Hemodyn instability	2	Pts randomized to receive Ultrafiltration x 24-48hrs +/- 1. ACE-Is/ARBs 2. B-Blockers 3. Digoxin 4. Nesiritide
Constanzo, et al., 2007	RCT	200	> 18	Age > 18 & at least 2 of the following: 2+ peripheral edema; JVD $\geq$ 7 cm; Ascites; Pulm edema or pleural effusion; Rales or PND	ACS Unattainable venous access Systolic BP $\leq$ 90 mmHg Serum Creatinine > 3 HCT > 45% Vasoactive drug use Systemic infection Heart transplant	20	Pts randomized to receive Ultrafiltration x 48 hrs
Rogers, et al., 2008	RCT	26	> 18	Age > 18 EF < 40% > 2+ pitting edema of LE JVP > 10 cm Ascites PND $\geq$ 2 pillow orthopnea Pulm edema or Pleural effusion	ACS Systolic BP $\leq$ 90mmHg Serum creatinine $\geq$ 3 mg/dL HCT > 45% Unattainable venous access Clinical instability likely to require nitrprusside.	5	Pts randomized to receive Ultrafiltration x 48 hrs +/- * 1. ACE-Is/ARBs 2. B-Blockers 3. Spironolactone 4. Digoxin *only used if pts were on these meds prior to hospitalization

Table 2 outlines the main endpoints measured in the **Costanzo 2007** study which compared ultrafiltration (UF) to intravenous diuretics (IVD) for symptom management and number of rehospitalizations for congestive heart failure symptoms. Weight loss, dyspnea and rate of recidivism are all endpoints that are both extremely important and evident to patients. One of the primary objectives of the study was to show that in hypervolemic patients hospitalized with congestive heart failure, ultrafiltration can produce greater weight loss over a given period of time versus intravenous diuretics. At 48 hours, weight loss was greater in the ultrafiltration group than in the intravenous diuretic group with a statistically significant p-value of 0.001, evaluated with the Wilcoxon's rank sum test.[5]

Dyspnea scores rated by patients on a scale of 1 through 7, 1 being markedly worse and 7 being markedly better, proved similar between the UF and IVD groups, with the mean dyspnea scores being 5.4 and 5.2 respectively leaving a p-value lacking statistical significance (0.588). Finally, at 90 days post-discharge, the UF group had 16 of 89 patients rehospitalized (18%) versus the IVD group with 28 of 87 being rehospitalized (32%) for CHF-related symptoms, giving a p-value approaching statistical significance at 0.037%, calculated with the Kaplan-Meier analysis. Although the relative risk reduction or relative benefit increases could not be calculated here for weight loss or dyspnea, we were able to see a 20.6% relative benefit increase for UF patients calculated based on the number of patients in the study that were *not* rehospitalized for CHF-related symptoms. [5]

Table 2. Comparison of weight loss and dyspnea scores in pts after 48 hours and 8 hours respectively between UF and IV Diuretics and how volume reduction affects recidivism.

Costanzo 2007 Mean weight loss and dyspnea scores evaluated by Wilcoxon rank sum test and the beneficial effects of UF v IVD on rehospitalization.

	Baseline UF[a]	Baseline IVD[b]	UF Wt Loss	IVD Wt Loss	P-value
Weight (kg)	101 ± 27	96 ± 29	5.0 ± 3.1	3.1 ± 3.5	0.001
	Baseline UF	Baseline IVD	UF	IVD	P-value
*Dyspnea Score (1-7)	3-7	1-7	5.4 ± 1.1	5.2 ± 1.2	0.588

	Baseline Pre-UF	Baseline Pre-IVD	90 days post - UF	90 days post - IVD	P-value	RBI[c]	ABI	NNT
Hospitalizations for CHF	1.6 ±1.9	1.5 ± 1.7	18%	32%	0.037	20.6%	14%	8

* Dyspnea scores were measured from 1 through 7; 1 being markedly worse and 7 being markedly better

[a] UF – Ultrafiltration

[b] IVD – Intravenous Diuretics

[c]RBI, ABI & NNT values were calculated based on "# of CHF patients *not* rehospitalized for CHF symptoms".

In **Table 3** we see the effect of UF and IVD on fluid loss after 48 hours as reported in the **Rogers 2008** study. This study pointed out that some patients may have diuretic resistance and this could account for the difference in renal function and subsequently fluid removal in the Furosemide group versus UF. All continuous variables in this study were reported as mean ± standard deviation. The group comparisons were

made using a paired *t*-test (2-tailed) and differences between the treatment groups evaluated with the Fisher exact test. For net fluid removal at 48 hours, which included urine output *plus* ultrafiltrate for the UF group, p = 0.682 and for weight loss p = 0.85 as the numbers between the UF and Furosemide groups were very similar, and therefore, not statistically significant.[3]

Table 3. Effect of UF and IVD on Fluid Loss after 48 hours

Rogers 2008 Fluid Loss and subsequent weight loss of CHF patients given IV Furosemide vs UF			
	UF	IVD[a]	**P-value[b]**
*Net Fluid Loss	5864 ± 2414	5786 ± 2587	0.682
	UF	IVD	**P-value**
Weight Loss	2.2 ± 2.6	1.9 ± 2.7	0.850

*Net Fluid loss was measured in mL as total urine output after 48 hrs for IVD group and as ultrafiltrate plus urine output for the UF group.
[a] Furosemide dose over 48 hrs ranged from 240-520mg
[b] **P-values:** Unpaired *t*-test was used for comparisons between treatment groups and differences were evaluated with the Fisher exact test. RRR, ARR, and NNT values could not be calculated due to having only continuous data.

Table 4 shows results from **Bart 2005.** Although this study was ultimately measuring weight loss, the p-value ended up not being statistically significant (0.240). UF proved more favorable, however, for reduction of dyspnea (p = 0.039) and global CHF symptoms (p= 0.023) suggesting that fluid removal may be more effective with UF vs. usual care methods such as IV diuretics and inotropes.[4] In addition, 56.3% of UF patients reported "marked improvement" in global CHF symptoms versus 18.8% in the usual care group, and 31.3% of those treated wth UF reported "marked improvement" with dyspnea compared to 18.8% of those treated with usual care.[4]

Table 4. Symptom reduction comparisons in CHF patients treated with UF and "usual care"

Bart 2005 Percent of persons who reported improvements or no change in CHF symptoms, specifically dyspnea, after 48 hours of treatment.						
Global CHF Sx	UF	UC[a]	P-value[b]	RBI	ABI	NNT
Marked Improvement	56.3%	18.8%	0.023	18.1%	10.5%	10
No Change	6.3%	18.8%				
Dyspnea Sx	UF	UC	P-value	RBI	ABI	NNT
Marked Improvement	31.3%	12.5%	0.039	55.5%	26.3%	4
No Change	6.3%	37.5%				

[a] – UC = Usual Care group was treated primarily with IV diuretics, but IV inotropes were also used in several patients.
[b] – P-values: Two-sided Wilcoxon rank sum test was used since this data was continuous.

Table 5 shows adverse events and NNH values. Only two of the three trials used included information about adverse events along with their data. Common to both studies was infection related to catheter site and occurred in 1 of 19 patients in the **Bart 2005** study and in 1 of 89 in the **Costanzo 2007** study; both events were minor and did not exclude that person from the study.[4,5] Catheter-related infection was the only adverse event reported in the 2005 study. Hypotension was the most commonly reported adverse event in **Costanzo 2007**, though no one dropped out of the study or was excluded because of it. Other adverse events reported in the 2007 study were worsening heart failure, cardiac arrest, arrhythmias, and anemia, but it is impossible to pinpoint UF or

IVD as the causative factor of these events, especially taking into consideration the baseline health status of the patients enrolled in the clinical trial.[5]

Table 5. ***Adverse Events**

Costanzo 2007 N=89 (UF), N= 87 (IVD)			**Bart 2005 N=19 (UF), N=19 (Usual Care)**	
	UF	IVD	UF	UC
Infection (catheter-related)	1 (1%)	0	1 (5%)	0
Hypotension	22 (25%)	10 (11%)	∅	∅
Arrhythmias	10 (11%)	6 (7%)	∅	∅
Cardiac arrest	4 (4%)	6 (7%)	∅	∅
NNH	**8** Hypotension	-	**19** Infection Catheter-related	-

***Adverse events were not reported in **Rogers 2008** study
∅ - events not reported in study

Discussion:

Ultrafiltration is a non-drug based treatment option for congestive heart failure that can remove up to 1 lb per hour of excess volume from the blood. It can be compared to dialysis in that blood is moved extracorporeally, filtered of only sodium and water, and then returned to the body. The volume of blood cycled is, however, much less compared to hemodialysis leading to less incidence of hemodynamic instability. 88% of heart failure patients are currently being treated with intravenous diuretics but many patients develop diuretic resistance.[4] It is for these patients that ultrafiltration is currently being utilized most. The machine attached peripherally to the patient filters the blood through a semipermeable membrane by way of a pressure gradient system. The rate at which fluid is removed through the semipermeable membrane can be selected based on the patients' hemodynamic conditions. If patients become hypotensive, which did occur in the

Costanzo 2007 trial, it is possible to slow the rate of blood flow or ultrafiltration to avoid hemodynamic instability.[6]

While the costs of ultrafiltration exceed those of intravenous diuretics inititally, the thought is that reduction in length of hospital stays and decreased rates of recidivism will actually even out the cost discrepancy between the two treatment modalities. Monetary information, though very relevant, was not mentioned in any of the three RCTs studied.

All RCTs effectively demonstrated that in heart failure patients with volume overload, ultrafiltration results in greater fluid removal and is not associated with harmful adverse events. The most obvious limitations to all RCTs studied were the very small sample sizes. Furthermore, a more defined sample population needs to be studied to accurately determine rate of rehospitalization. The admission criteria utilized for these RCTs was very broad. Hospital readmission rates, for example, might be less favorable if the population studied were restricted to only class IV heart failure patients.

Conclusion:

While ultrafiltration has proven to be a safe alternative to intravenous diuretics for the treatment of heart failure, there is not enough consistent, significant data to say that it can be used as primary treatment. Further studies with a larger, yet more refined sample populations should be included. The age requirement should be 65 and older to better reflect the core heart failure population. Studies should further split intervention groups into the NYHA classes of heart failure III and IV. These changes will aid in proving true long-term efficacy and cost-effectiveness.

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