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Original Research Article

Peritoneal ultrafiltration: bridging the treatment gap to cardiac transplantation in refractory congestive heart failure management

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ABSTRACT

Background: Peritoneal ultrafiltration needs consideration as a therapeutic option for improvement in echocardiographic parameters, tissue Doppler imaging, and patient clinical status in patients with refractory congestive heart failure.
Methods: This prospective, non-randomised, two-year observational study from June 2012 to June 2014 included 19 clinic outpatients and in-patients admitted to the CARE hospital, Hyderabad. Baseline data was compared on initiation and after three months of ultrafiltration therapy. Out of 19 patients studied initially, 16 were alive and undergoing CAPD at 3 months.
Results: 3 months post ultrafiltration, the ejection fraction (EF) improved significantly from 35.4±6.6 to 43.1±13.8 ($p<0.01$), right atrial volume index (RAVI) decreased significantly from 31.8±14.3 to 28.3±14.9 ($P=0.016$), inferior vena cava (IVC) diameter decreased significantly from 2.27±0.44 to 1.8±0.68 ($P=0.01$), pulmonary artery systolic pressure (PASP) decreased significantly from 50.7±14.4 mmHg to 38.1±15.6 mmHg ($P<0.01$), hospitalisation days decreased significantly from 17.5±8.3 to 1.7±3.4 days ($P<0.0001$) and the distance covered in the 6 minutes' walk test (6MWT) increased significantly from 58.52 m±47.6 m to 176.4 m±80.7 m ($p<0.0001$). Except for 3 (17.6%) patients, significant patients that were NYHA class III and IV improved to NYHA class I and II ($p<0.0001$; Table 1).
Conclusions: Ultrafiltration was safe and associated with significant improvements in echocardiographic parameters, NYHA functional class, physical performance (6MWT), and reduction of hospitalization days in patients with refractory congestive heart failure.

Keywords: CAPD, Diuretics, Echocardiography, Ultrafiltration, Refractory Heart Failure

INTRODUCTION

Heart failure is a major growing health problem. Major advances leading to newer therapies are being made in understanding the pathophysiology of heart failure as a chronic progressive disorder. Whatever the cause, all heart failure patients eventually progress to a refractory stage characterized by severe edema, worsening renal function and resistance to diuretic therapy. A logical treatment for this "cardiorenal syndrome" is the use of dialysis which efficiently treats both the hypervolemia and azotemia of refractory heart failure.

The use of loop diuretics is associated with many limitations such as elimination of hypotonic urine, diuretic resistance, lack of dosing guidelines, electrolyte abnormalities, reduced glomerular filtration rates, and direct neurohormonal activation. Neither has the safety nor the efficacy of loop diuretics been demonstrated in randomized controlled trials. Adverse events such as photosensitivity, skin rashes, hearing loss, and bone loss have been known to occur with the use of loop diuretics.

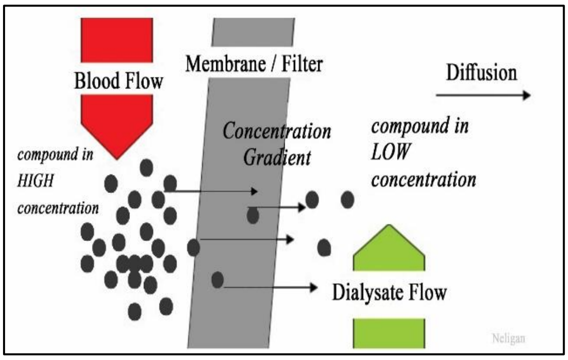

Figure 1: Diffusion / dialysis: the movement of solutes from a compartment of high concentration to one of lower concentration – along an electrochemical gradient.

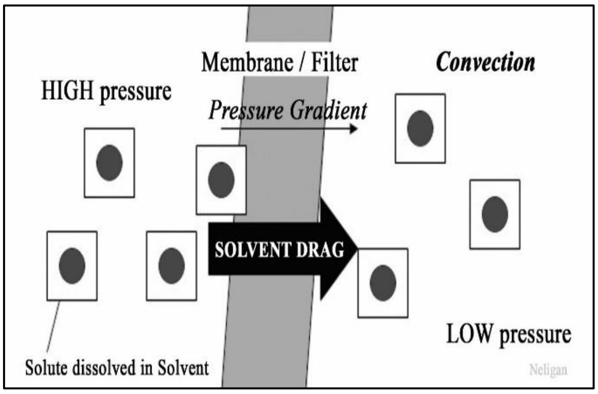

Figure 2: Convection / ultrafiltration – solute is carried (in solution) as a fluid across a semipermeable membrane in response to a transmembrane pressure gradient (a process known as solvent drag). This mimics what actually happens in the normal human kidney. This is very effective in removal of fluid and middle-sized molecules, which are thought to cause uremia. Moreover, most of the cytokines involved in sepsis are "middle molecules".

Although all modalities of dialysis have been tried, peritoneal dialysis (PD) is the simplest choice, and it offers several advantages. Peritoneal ultrafiltration is an already established long-term home-based therapy that is associated with preservation of residual renal function, gentle continuous ultrafiltration, hemodynamic stability, sodium sieving with maintenance of normonatremia, and perhaps with less inflammation than hemodialysis, especially with newer PD solutions. Clearance of middle molecules could be important. Many cytokines and humoral factors have been implicated in the progression of heart failure.[1] Ultrafiltration provides several advantages which include removal of isotonic plasma water, precise control of rate and amount of fluid removal, no effect on plasma concentration of electrolytes, improved glomerular filtration rate, no direct neurohormonal activation. Randomized controlled trials demonstrating safety, efficacy, and improved outcomes of ultrafiltration are also available. In this particular setting, intermittent ultrafiltration has emerged as an alternative therapeutic option for reducing volume overload, with potential advantages over standard treatment in acute situations. In this study we analysed the effect of ultrafiltration on echocardiographic parameters using a two-dimensional echo, and tissue Doppler imaging at baseline and at three-month post ultrafiltration. We also studied the effect of ultrafiltration on functional status changes in the NYHA class, 6MWT and various blood parameters.

Ultrafiltration has proven to be a useful tool in the treatment of volume overload, with or without renal insufficiency. The technique evolved as physicians sought to preserve hemodynamic stability and expedite volume removal in patients' refractory to diuretics. As such, a higher total volume can be removed safely, over longer durations of ultrafiltration.

METHODS

This was a non-randomised observational study conducted prospectively on a cohort of patients followed in the heart failure unit and nephrology unit of the CARE hospital, Hyderabad, over a period of 2 years from June 2012 to June 2014. The study population included both outpatients who attended the heart failure clinic, and inpatients admitted with heart failure.

Baseline data was collected initially, and then again after three months of ultrafiltration therapy.

The bags used for peritoneal dialysis were 1.5% dianeal bags (2000 ml) and 2.5% dianeal bags (2000 ml). Most of them were on one or two exchanges per day with an aim to get ultrafiltration of around 1000-1500 ml per day. The peritoneal ultrafiltration prescription was later optimised by the nephrologist based on the fluid overload state of the patient.

Patients with NYHA functional class III/IV; patients with refractory heart failure i.e. patients who have marked symptoms at rest, or on minimal exertion, despite optimal medical therapy with EF (ejection fraction) <45%; and, patients that met any one of the two following criteria were considered as fulfilling the inclusion criteria. 1. Persistent dyselectrolytemia (hyponatremia or hypokalemia), or 2. At least one previous hospitalization for acute heart failure in the previous 3 months.

Patients with heart failure associated with systemic disorders, systemic lupus erythematosus, malignancy, end-stage liver disease, severe chronic respiratory disease, and any other abdominal pathology in which ultrafiltration is contraindicated were considered as part of the exclusion criteria. Patients that were also part of the exclusion criteria were those that with an ejection fraction [EF] >45%, end stage renal disease (eGFR<15 mL/min/1.73 m2), acute coronary syndrome and those unable to give valid written consent.

After satisfying the inclusion and exclusion criteria, and after informed consent, patients were enrolled in study. To measure the success of ultrafiltration, the endpoints were defined by changes that occurred in pre- and post-ultrafiltration study variables at 3 months. The collected data was entered and analyzed using Microsoft Office Window Excel 2007 and Statistical package for social sciences (SPSS) version 16 (SPSS 16.0 for Windows, release 16.0.0. Chicago: SPSS Inc). We considered the association or difference to be significant when the p value was less than 0.05. The study conformed to widely accepted ethical principles guiding human research (such as the Declaration of Helsinki) and had been approved by a local ethics committee.

RESULTS

A total of 19 patients with refractory heart failure of various etiologies were studied, 17 (89.4%) males, and 2 (10.6%) females (Table 1). Out of the 19 patients, 16 were alive and underwent CAPD at 3 months. Most of the patients 17 (89.5%) suffered from hypertension, followed by diabetes 15 (78.9%) and thyroid disorder 7 (36.8%).

Table 1: Study parameter changes pre- and post-ultrafiltration.

Parameters	Pre-ultrafiltration* (n= 17)	Post-ultrafiltration * (n=17)	Mean diff.*	't'- value (n=16)^	P value
LVIDDI	5.77±0.65	5.57±0.74	-0.20±0.47	1.75	0.09
LVIDSI	4.62±0.8	4.35±1.04	-0.27±0.68	1.65	0.117
LVEDVI	64.55±16.2	61.7±19.7	-2.8 ±10.5	1.09	0.29
LVESVI	40.11±14.12	36.4±17.4	-3.7±9.2	1.64	0.119
EF Simpsons	35.4±6.6	43.1±13.8	7.64±10.4	3.02	0.008@
RAVI	31.8±14.3	28.3±14.9	-3.52±5.3	2.69	0.016@
LAVI	31.65 ±9.6	30.8±9.8	-0.82±3.7	0.9	0.38
IVC	2.27±0.44	1.8±0.68	-0.47±0.48	3.99	0.001#
Parameters	Pre-ultrafiltration * (n= 17)	Post-ultrafiltration * (n=17)	Mean diff.*	't'- value (16)^	P- value
Weight (kg)	67±9.11	66±10.11	-1.0±11.7	0.332	0.744
BSA	1.75±0.1	1.72±0.11	-0.024± 0.06	1.52	0.147
BMI (kg/m^2)	24.9±2.7	24.2±3.5	-0.77±2.2	1.4	0.172
6min walk test (6MWT) (metres)	58.52± 47.6	176.4±80.7	117.9±86.1	5.64	0.0001#
Duration of stay in hospital (days)	17.5±8.3	1.7±3.4	-15.7±9.2	7.01	0.0001#
Hospitalization rate	17 (100%)	5 (29.4%)	Chi-square =15.54, df=1		0.0001#
Diuretic use	19 (100%)	4 (23.5%)	Chi-square =19.54, df=1		0.0001#
NYHA Class III and IV	19 (100%)	3 (17.6%)	Chi-square =22.25, df=1		0.0001#

*** = mean±SD, # = Highly significant, @ = significant, ^ = paired t- test, '-' minus value in front of mean diff. signify reduction in the value after dialysis. LVIDDI = Left Ventricular Internal Diameter Diastolic Index; LVIDSI = Left Ventricular Internal Diameter Systolic Index; LVEDVI = Left Ventricular End Diastolic Volume Index; LVESVI = Left Ventricular End Systolic Volume Index; EF = Ejection Fraction; RAVI = Right Atrium Volume Index; LAVI = Left Atrium Volume Index; IVC = Inferior Vena Cava; BSA = Body Surface Area; BMI = Body Mass Index; NYHA = New York Heart Association**

The commonest cause for heart failure was ischemic heart disease (ISCH) 13 (68.4%), followed by idiopathic dilated cardiomyopathy (DCMP) 21.1%, arrhythmogenic right ventricular dysplasia (ARVD) (5.3%), and chronic rheumatic heart disease (CRHD) (5.3%).

Coronary artery disease (CAD) was previously confirmed by the coronary angiography reports of the patients. The end diastolic dimension index in patients before the treatment was 5.77±0.65 mm and 5.57±0.74 mm (S.D of -0.20±0.47 mm) at the end of 3 months (p=0.09). The ejection fraction (EF) before the treatment was 35.4%±6.6%, and after the treatment at the end of 3 months it was 43.1%±13.8% and corresponding to a mean difference of 7.64%±10.4% (p<0.01; Table 1).

The improvement in ejection fraction was due to a decrease in the preload secondary to effective decongestion by peritoneal ultrafiltration. The other possible contributing factors could be removal of myocardial depressant factors, and interruptions in the vicious cycle of neurohormonal activation (RAAS).

Sanchez et al. found ejection fraction improvements from a mean of 33%±3% to 36%±4% six months post ultrafiltration in his study of seventeen patients, although this was not found to be statistically significant, p=0.007.2 Elhalel-Dranitzki et al and Bertoli et al. found similar improvements in EF in their studies.[3,4]

A mean difference of -0.47±0.48 cm was seen in the IVC diameter, from 2.27±0.44 cm before the treatment, to 1.8±0.68 cm at the end of 3 months (p=0.01; Table 1).

The duration of hospitalization days for acute heart failure before ultrafiltration was 17.5±8.3 days, and this reduced very significantly post ultrafiltration to 1.7±3.4 days (p<0.0001; Table 1). Similar improvements were found by Stegmayr et al, Elhalel-Dranitzki et al, Bertoli et al, Gotloib et al. and Julio Nunez et al.3-7

Diuretic usage was seen in 19 (100%) patients before the treatment, and this reduced to 4 (23.5%) at the end of 3 months, which was significant (p<0.0001; Table 1).

DISCUSSION

19 (100%) NYHA class III and IV HF patients significantly improved post ultrafiltration to NYHA class I and II with the exception of 3 (17.6%) (p<0.0001; Table 1). This may be due to the optimal decongestion experienced with peritoneal ultrafiltration, improvements in cardiac systolic and diastolic parameters, and appropriate adjustments of the ultrafiltration cycle. Similar findings were concluded by Chung et al and Mehrotra et al and may be correlated to symptomatic improvement in NYHA class.[8,9]

With improving status, BP reduction with the help of beta-blockers (BB) like Metpure XL helped achieve target HR due to improvement in hemodynamics. BB was uptitrated according to the tolerance of the patients, this was possible due to improvement in their hemodynamics which further improved their functional status.

There were highly significant increases in the 6-MWT from a mean of 58.52±47.6 m pre-treatment distances to distances of 176.4±80.7 m post ultrafiltration (p<0.0001).

NT-proBNP levels were significantly reduced from pre-treatment levels of 1582.6±1261.7 pg/mL to 528.6±627.5 pg/mL post ultrafiltration (Table 1).

Looking at the effect on renal function, there was no significant decrease in serum urea, serum creatinine and eGFR at the baseline and the three months visit post ultrafiltration.

During a median follow-up of 3 months, 4 episodes of peritonitis in four patients were registered, accounting for 21% of the total study population of which 3 responded to antimicrobial therapy. One death resulted from septic shock secondary to peritonitis. One patient had a procedure related complication that manifested as leakage through the catheter insertion site which was treated. One patient expired at home. One patient died in hospital due to refractory congestive failure followed by ventricular tachycardia. We attribute these deaths to their older age, and high prevalence of co-morbidity in these patients. Most cases were treated in an ambulatory setting without major clinical consequences, except one patient, who died due to ultrafiltration related abdominal infection.

In refractory heart failure, the predominant pathophysiology is sodium and fluid retention, and azotemia resulting from renal hypoperfusion with inadequate response to traditional medical therapy. A logical treatment is ultrafiltration, which is efficient in treating both the hypervolemia and azotemia of refractory heart failure.

This preliminary study indicates that ultrafiltration is a feasible alternative for the treatment of symptomatic patients with advanced CHF, persistent fluid overload (despite loop diuretic therapy), with or without co-existence of renal failure but excluding patients with ESRD. Echocardiography is a good tool in assessing the effect of ultrafiltration.

Clearance of middle molecules could be important. Many cytokines and humoral factors have been implicated in the progression of heart failure. Many of these cytokines—for example, interleukin-1 and TNF—also are known to have a myocardial depressant effect. The molecular weights of these substances range between 500 Da and 30000 Da, which means that they are removable by PD.

NT-proBNP is a small molecule that can be filtered by the peritoneal route. However, reductions of NT-proBNP alone may not cause symptomatic relief. We understand that clearance of middle molecules (myocardial depressant factors) and ultrafiltration were both responsible for symptomatic improvements in heart failure. We have not done the dialysate NT-proBNP level to demonstrate the peritoneal clearance in this study.

Zemel et al showed the appearance of TNF-α and soluble TNF receptor 1 and 2 in PD effluent and this may contribute to improvement in ejection fractions.[10]

We would like to stress that in this population of patients with advanced refractory CHF, this risk appears acceptable given the elevated baseline risk of these patients when treated with the usual-care approach. As per the natural history of heart failure, the mortality following hospitalization for patients with heart failure is 10.4% at 30 days, 22% at 1 year, and 42.3% at 5 years, despite marked improvement in medical and device therapy. Each re-hospitalization increases mortality by about 20-22%. Mortality is >50% for patients with NYHA class IV, and ACC/AHA stage D heart failure.[11]

The clinical relevance of our findings stems from the fact that this is a non-traditional approach used for the treatment of a population with a prohibitively high morbidity/mortality, and where most of the pharmacological treatments are often contraindicated, not tolerated, or have failed to improve symptoms or prognosis. Ultrafiltration by peritoneal route would provide an option to a patient with refractory heart failure waiting for cardiac transplant.

Although all modalities of dialysis have been tried, PD is the simplest choice, offering several advantages.[1,12-13] As compared with hemodialysis, PD is associated with preservation of residual renal function.[14] Gentle continuous ultrafiltration offers hemodynamic stability, and better middle-molecule clearance.[15] Clearance of middle molecules could be important. Many cytokines and humoral factors have been implicated in the progression of heart failure. Many of these cytokines-for example, interleukin-1 and TNF-also are known to have a myocardial depressant effect.[16] The molecular weights of these substances range between 500 Da and 30000 Da, which means that they are removable by PD. Zemel et al. showed the appearance of TNFα and soluble TNF receptor 1 and 2 in PD effluent.10 Sodium sieving has been linked to the maintenance of normonatremia and, maybe, a reduction in inflammation, particularly with the newer PD (icodextrin) solutions.

CONCLUSION

PD is well established as a home-based long-term therapy that does not require complex machinery or hospital resources. Hemodynamic stability and middle-molecule clearance are improved with gentle continuous ultrafiltration by the peritoneal route. Ultrafiltration is therefore a good alternative to patients with refractory heart failure waiting for cardiac transplant.

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