Original Article

Ultrafiltration by Peritoneal Route in Refractory Chronic Congestive Cardiac Failure

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Abstract

Diuretics are the mainstay of treatment of refractory heart failure. There is a high incidence of dyselectrolytemia and suboptimal response due to diuretic resistance. Ultrafiltration by peritoneal route can be a safe and effective alternative. This study aims to study the ultrafiltration by peritoneal route in refractory heart failure patients with respect to change in functional status, renal parameters, left ventricular ejection fraction, number of days of hospitalization, and level of myocardial depressant factors. This was a prospective observational study conducted in Nephrology Department of tertiary care hospital. We studied patients with refractory heart failure who had persistent symptoms requiring frequent admissions despite optimal medical decongestion or had dyselectrolytemia with worsening renal parameters. The data were collected at baseline and then after 6 months of starting ultrafiltration. A total of 30 participants were studied. All the patients were in NYHA functional status Class IV before peritoneal ultrafiltration. There was a significant improvement in functional status and only 14 patients (46%) had Class III to Class IV status after application of ultrafiltration. ($P < 0.001$) There was a significant improvement in duration of hospital stay (75.8 ± 43.3 days to 7.8 ± 12.4, $P > 0.001$), serum creatinine (3.18 ± 0.98 to 2.16 ± 0.79 mg/dl, $P < 0.001$), and left ventricular ejection fraction [29.3 ± 7.4 (%) to 48.5 ± 11.8 (%), $P < 0.0001$] post ultrafiltration. There was also significant improvement in level of myocardial depressant factors (IL-1, IL-6, TNF alpha). Ultrafiltration by peritoneal route seems to be an effective alternative and should be offered to patients with chronic heart failure who are symptomatic despite maximal medical treatment.

Keywords: *Diuretic resistance, myocardial depressant factors, New York Heart Association functional status, peritoneal ultrafiltration, refractory heart failure*

Introduction

The earliest descriptions of heart failure date back >3500 years to the Egyptian civilization. Even then, symptoms were correctly attributed to volume excess.[1] Today, it is understood that sodium retention in heart failure is under the influence of the sympathetic and renin-angiotensin-aldosterone systems.[2] The standard therapy of congestive heart failure (CHF) includes diuretics – mainly loop diuretics combined with spironolactone in patients with glomerular filtration rate (GFR) >30 ml/min/1.73 m^2, as well as sodium-blocking agents exerting their activity in other parts of the nephrons. Diuretics in the treatment of CHF induce salt and water removal in a way that results in hypotonic urine, a temporary reduction of hydrostatic pressure and natriuresis. Reports suggest that long-term treatment with loop diuretics might result in electrolyte wasting, renal dysfunction, and the progression of HF.[3,4] The efficacy of extracorporeal ultrafiltration was shown in EUPHORIA,[5] RAPID-CHF,[6] and UNLOAD[7] trials. The acute stress on myocardium due to subclinical ischemia and proinflammatory state[8] due to exposure to the bioincompatible membrane during hemodialysis can be avoided using the peritoneal route.[9]

The present study was conducted to evaluate the effect of peritoneal ultrafiltration on New York Heart Association (NYHA) functional status, days of hospitalization, renal parameters, left ventricular ejection fraction, and change in the level of myocardial depressant factors.

Subjects and Methods

This was an open-label prospective study conducted in Nephrology Department of Care Hospital, Hyderabad. The study

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was approved by ethical committee of the hospital. The inclusion criteria are as follows:

Patients with refractory heart failure who are symptomatic despite maximal medical therapy who have one of the following:

1. Presence of dyselectrolytemia
2. Two or more hospitalization in the past 6 months.

The patients who were willing to give consent and participate were enrolled in the study. They first underwent minimum two sessions of ultrafiltration by slow low-efficiency dialysis or slow continuous ultrafiltration over 48 h.

The Tenckhoff peritoneal dialysis catheter was inserted for peritoneal ultrafiltration. They were started on ultrafiltration on the same day. Initially, automated peritoneal dialysis machine was used. This was changed to manual exchange once the patient was shifted to the room. The prescription was individualized depending on the volume status of the patient. The demographic data, functional status (NYHA class), hemoglobin, serum creatinine, left ventricular ejection fraction, number of days of hospitalization, and level of myocardial depressant factors (interleukin-1 [IL-1], IL-6, tumor necrosis factor-alpha [TNF-α], NT-pro-BNP) were assessed pre- and post-ultrafiltration (after 6 months).

Statistical analysis

The collected data were entered and analyzed using Microsoft office window excel 2007 and SPSS version 16 (SPSS 16.0 for Windows, release 16.0.0., SPSS Inc., Chicago, IL, USA). Frequencies of all variables were taken to check frequencies. Mean and standard deviation were calculated for continuous variables. To show the mean difference in pre- and post-level, paired *t*-test was applied on the continuous grouped data while in grouped categorical data, McNemar's Chi-square test was applied. We considered the association or difference to be significant when the $P < 0.05$.

Results

A total of 30 participants were studied, 21 (70%) were males while 9 (30%) were females. The mean age of study participants was 62.56 ± 7.5 years (range 49–83 years). The average ultrafiltration was 1-1.5 liter per day with 1-2 exchanges per day on an average. Thus, after ultrafiltration, 30 pairs were studied for the effect [Tables 1 and 2].

All the subjects studied had cardiorenal syndrome type 2. They were studied for symptomatic improvement in form of change in NYHA functional status and days of hospitalization along with various biochemical parameters including hemoglobin, serum creatinine and level of myocardial depressant factors. The results of the change in clinical and biochemical parameters are summarized in the table [Tables 1 and 2]. Most of the patients had frequent hospitalization due to heart failure. There was a significant improvement in duration of hospital stay from a mean of 75.8 ± 43.3 days to 7.8 ± 12.4 days post ultrafiltration. This was statistically significant with $P = 0.0001$. Seventeen patients out of thirty did not require hospitalization due to heart failure during the study period. The hemoglobin level improved from a mean value of 9.1 ± 1.17 to 10.7 ± 1.5 (g/dl). The mean serum creatinine of 3.18 ± 0.98 improved to 2.16 ± 0.79 mg/dl ($P < 0.001$). All the patients had SOB at rest (NYHA class IV) at the time of enrolment. The functional status improved and only 14 patients (46%) had Class III to Class IV status after application of ultrafiltration. ($P < 0.001$) The ejection fraction improved from a mean of 29.3 ± 7.4(%) to 48.5 ± 11.8(%) post ultrafiltration ($P = 0.0001$). The level of myocardial depressant factors (IL-1, IL-6 and TNF-alpha) decreased post-ultrafiltration ($P < 0.001$). There was also a significant reduction in the level of NT-pro-BNP ($P < 0.0001$).

Table 1: Therapeutic role of ultrafiltration in improving patient clinical status

Parameters	Pre-ultrafiltration (*n*=30)	Post-ultrafiltration (*n*=30)	*p*
Hb (g/dl)	9.1±1.17	10.7±1.5	0.0001
Ejection fraction (%)	29.3±7.4	48.5±11.8	0.0001
Duration of stay in hospital (days)	75.8±43.3	7.8±12.4	0.0001
Hospitalization rate (%)	30 (100)	13 (43.4)	0.0001
NYHA Class III and IV (%)	30 (100)	14 (46.6)	0.0001

Hb: Hemoglobin, NYHA: New York Heart Association

Discussion

With an increasing number of patients worldwide developing both CHF and chronic kidney disease (CKD), the coexistence of these two conditions has become a matter of concern.[10,11] Whatever the cause, all heart failure patients eventually progress to a refractory stage characterized by worsening renal function and resistance to diuretic therapy with attending severe edema.[12] We studied the effect of peritoneal ultrafiltration in these patients with chronic refractory congestive cardiac failure.

A total of 30 patients with refractory chronic CHF were included in the study. All the patients ($n = 30$) were in NYHA functional status Class IV before peritoneal ultrafiltration. There was a significant improvement in functional status, and only 14 patients (46%) had Class III to Class IV status after application of ultrafiltration. The similar improvement of NYHA functional status of Class 1–2 was observed in previous studies.[13-18] The improvement in functional status was probably secondary to improvement in the left ventricular ejection fraction,

Table 2: Effect on level of myocardial depressant factors and N-terminal pro-brain-type natriuretic peptide before and after ultrafiltration

Parameters	Preultrafiltration (*n*=30)	Postultrafiltration (*n*=30)	Mean difference	*p*
IL-1	24.1±14.7	8.1±4.04	−15.9±12.1	0.0001
IL-6	130.6±155.4	23.7±17.6	−106.8±156.5	0.001
TNF-α	44.6±12.06	14.9±5.07	−29.7±10.5	0.0001
NT-pro-BNP	3917.5±4575.6	506.6±594.9	−3410.8±4620.4	0.0001

NT-pro-BNP: N-terminal pro-brain-type natriuretic peptide, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha

increase in hemoglobin level, and optimal decongestion achieved with peritoneal ultrafiltration.

There was a significant improvement in duration of hospital stay from a mean of 75.8 ± 43.3 days to 7.8 ± 12.4 days postultrafiltration. This was statistically significant (P = 0.0001). Seventeen patients out of thirty patients did not require hospitalization due to heart failure during the study period. This was similar to observation in the study by Courivaud *et al*.[17] They observed a significant reduction in the number of days of hospitalization for acute decompensated heart failure after peritoneal ultrafiltration initiation (3.3 ± 2.6 days/patient–month vs. 0.3 ± 0.5 days/patient–month, $P < 0.0001$). Hospitalization time for cardiovascular causes was 13.7 ± 26.5 days/patient/month before and 3.5 ± 8.8 days/patient/month after starting dialysis (P = 0.001), equivalent to a 74% reduction in a study by Cnossen *et al*.[19] Similar findings were observed in studies by Bertoli *et al*.,[20] Ryckelynck *et al*.,[16] Gotloib *et al*.,[13] Sánchez *et al*.,[21] and Elhalel-Dranitzki *et al*.[19] with a significant decrease in number of days of hospitalization postperitoneal ultrafiltration. This reduction can be considered an indirect marker of improved quality of life in the patients and also a surrogate marker of better control of heart failure symptoms.

There was renal dysfunction at baseline with a mean serum creatinine of 3.18 ± 0.98. Postultrafiltration, the mean serum creatinine improved to 2.16 ± 0.79. This was statistically significant with P = 0.0001. The improvement in renal parameter may be related to improvement in renal perfusion secondary to improved cardiac function, reduced neurohormonal activation, reduction of diuretic dosages, and solute clearance by peritoneal route. The patients were on variable prescription ranging initially from one to two exchanges every day to one exchange once in two or three days. This solute clearance may have contributed to decrease in creatinine although the exact clearance was not measured. The improvement in renal functions postultrafiltration was observed in the study by König *et al*.[14] with a change in mean serum creatinine from 2.7 (1.5–4.6 mg/dl) to 1.8 (1.1–3.1 mg/dl). Similar findings were observed in a study by Bertoli *et al*.[20] where the renal function was measured by Cockcroft–Gault formula whereas there was no significant change in renal function measured by MDRD equation in the study by Sánchez *et al*.[21]

There was improvement in left ventricular ejection fraction from a mean of 29.3 ± 7.4 (%) to 48.5 ± 11.8 (%) postultrafiltration, which was statistically significant (P = 0.0001). A similar finding was observed by Bertoli *et al*.[20] where there was improvement in the left ventricular ejection fraction postultrafiltration in their case study of two patients. König *et al*.[14] found improvement in the left ventricular ejection fraction postultrafiltration in their case study of three patients. In a study by Takane *et al*.,[22] of 16 patients, mean left ventricular ejection fraction before the start of peritoneal ultrafiltration was 31% ± 3%. Introduction to ultrafiltration was associated with a significant improvement in the left ventricular ejection fraction to 44% ± 6% ($P < 0.05$).

Ryckelynck *et al*.[16] performed echocardiography in eight of sixteen patients studied for the effect of ultrafiltration. The left ventricular ejection fraction was either stable (2 cases), improving (4 cases), or deteriorating (2 cases). Cnossen *et al*.[19] performed echocardiography in all patients before starting dialysis. Left ventricular ejection fraction was 33 ± 16%. A second echocardiography was performed in 18 patients. Ejection fraction was either stable (n = 2), improved (n = 11), or aggravated (n = 5). Mean ejection fraction at the second echocardiography was 34 ± 13 (%) which was not statistically significant. Sánchez *et al*.[21] found improvement in ejection fraction 6-month postultrafiltration in their study of seventeen patients from a mean of 33 ± 3 (%) to 36 ± 4 (%) with P = 0.007. The improvement in ejection fraction is due to decrease in preload secondary to effective decongestion by peritoneal ultrafiltration. The other possible contributing factor could be the removal of myocardial depressant factors.

There was an improvement in hemoglobin level postultrafiltration from a mean value of 9.1 ± 1.17 to 10.7 ± 1.5 (g/dl). All the patients were also on oral iron supplement for anemia treatment prior to enrolment and continued during study period. Erythropoiesis stimulating agents were also continued in patients with hemoglobin less than 10 gm/dl. A similar finding was observed in the study by Takane *et al*.[22] in 16 patients. They found significant increase in mean hemoglobin level from 8.5 ± 0.3 g/dl to 10.5 ± 0.5 g/dl ($P < 0.01$). In a study by Sánchez *et al*.,[21] there was an improvement in serum hematocrit level from the mean of 38 ± 4 to 40 ± 5, although it was not

statistically significant (P = 0.725). The improvement in hemoglobin was due to correction of the dilutional effect of fluid overload after decongestion. The other possible causes could be the removal of inflammatory cytokines by peritoneal ultrafiltration, which can cause bone marrow suppression, improvement in oral intake, and improved absorption of nutrients from gut after decongestion.

There was significant change in the level of various myocardial depressant factors (IL-1, IL-6, TNF-α) postultrafiltration. This is secondary to removal of these factors by peritoneal route. The removal of these factors by their appearance in peritoneal dialysis effluent was earlier demonstrated by Zemel *et al*.[23] There was a significant improvement in NT-pro-BNP which reflects improvement in cardiac failure.

Limitation

1. Nonrandomized study
2. Single-center study
3. Long-term follow-up is needed to assess long-term outcome such as survival benefit and persistence of clinical benefit.

Conclusion

Ultrafiltration by peritoneal route seems to be an effective therapy in patients with chronic refractory CHF. There was a significant improvement in left ventricular ejection fraction, and NYHA functional status, which is an indicator of the efficacy of peritoneal ultrafiltration. There was a significant reduction in a number of days of hospitalization and some of the patients never required hospitalization during the study period. Hence, peritoneal ultrafiltration should be offered to patients with chronic heart failure who are symptomatic despite maximal medical treatment.

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Conflicts of interest

There are no conflicts of interest.

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