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First Experience in Ambulatory Ultrafiltration Therapy for Congested Heart Failure Patients in Israel: A Feasibility Study

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ABSTRACT: **Background:** The prevalence of heart failure (HF) is increasing rapidly with high readmission rates, mainly due to fluid retention. Ultrafiltration (UF) is a mechanical method for removing fluids. Since UF was introduced only recently in Israel, the skill and experience required for outpatient congested HF patients is scarce.

Objectives: To evaluate the feasibility and safety of UF therapy in congested HF patients in outpatient clinics under a strict protocol of monitoring and therapy that we developed.

Methods: Between April and September 2013 we applied UF in our outpatient clinic to seven chronically congested HF patients with NYHA III-IV who did not respond adequately to diuretics. We administered a total of 38 courses.

Results: On average, 1982 ml fluid per course was removed without significant adverse events and with patients' subjective feeling of improvement. Only two courses were interrupted prematurely due to mechanical problems but were completed without harm to the patients.

Conclusions: Under appropriate professional medical supervision, UF therapy in an outpatient setting is a safe and effective procedure and serves as an additional tool for managing congested HF patients who do not respond adequately to diuretics.

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KEY WORDS: ultrafiltration (UF), heart failure (HF), outpatient, congestion, fluid retention

The prevalence of heart failure (HF) is increasing, along with a high readmission rate most commonly due to fluid volume overload [1]. While diuretics are a valid treatment for congestion, it is not uncommon to observe reduced effectiveness of loop diuretics with repeated exposure [2].

Ultrafiltration (UF) is an alternative method of sodium and water removal, with a sodium concentration in the ultrafiltrate equal to that in the water component of the plasma. Accordingly, while the fluid removed with diuretics is hypotonic, the ultrafiltrate is essentially iso-osmotic and isonatric compared with plasma. Therefore, for any amount of fluid withdrawn, more sodium is removed with ultrafiltration than with diuretics.

Technically, after cannulation of a vein, ultrafiltration is performed on blood extracted from and then returned to the patient via a separate access to the venous circulation. Ultrafiltration can be isolated, intermittent, or continuous. With appropriate ultrafiltration rates, the extracellular fluid gradually refills the intravascular space and blood volume is maintained. Ultrafiltration does not stimulate macula densa-mediated neurohormonal activation and does not produce prolonged intravascular hypovolemia because ultrafiltration removes fluid from the blood at the same rate at which fluid is reabsorbed from the edematous interstitium [3-5].

Several studies focusing on hospitalized HF patients demonstrated the utility of UF in HF patients admitted with acute HF [6,7]. Interestingly, despite its potential theoretical advantages over conventional diuretic treatment, UF was not superior in acute HF patients with cardiorenal syndrome [8]. Moreover, these studies focused mainly on UF administered in hospital settings; only a few studies were conducted with a small number of HF patients treated with UF in outpatient settings [9].

In Israel, UF has never been attempted in HF patients in ambulatory settings. The purpose of the current study was to evaluate the potential feasibility of UF in the ambulatory setting of a specialized HF clinic as a treatment for symptomatic HF patients with insufficient diuretic response, focusing on safety and technical operative factors. The study was approved by the Institutional Review Board of Clalit Health Services, the largest of Israel's four health insurance funds. All patients signed a written informed consent prior to their inclusion in the study.

PATIENTS AND METHODS

Between April and September 2013 we treated seven symptomatic New York Heart Association III-IV (NYHA III-IV)

chronically congested HF patients who did not clinically respond to diuretic regimens including previous intravenous therapies, as judged by their HF-treating cardiologist. Treatments were scheduled on a weekly basis.

Patients were denied UF therapy if they met any of the following criteria: age < 18 years, symptoms suspicious of acute coronary syndrome, creatinine level > 3 mg/dl in the week prior to the planned UF treatment, hemodynamic instability, hematocrit level > 45%, contraindication for anticoagulation treatment, or carrying a ventricular assist device. Patients' baseline characteristics are presented in Table 1.

UF PROCEDURE

We used the Aquadex FlexFlow TM System (CHF Solutions Inc., Brooklyn Park, MN, USA) for the UF therapy. Prior to any treatment session, a senior cardiologist examined the patients to verify the presence of congestion, clinical stability, and no recent deterioration in renal function tests over the previous week. The use of a diuretic was forbidden on the day of UF therapy.

UF cannula sets were flushed with 1500 units of heparin, and two peripheral (17 gauge) intravenous lines were inserted, each in a different arm at the antecubital fossa (the external jugular vein in one patient). The better position of the two lines was chosen as the inflow access, since we found the outflow cannula to be more technically challenging for operation of the device.

During the actual UF procedure, anticoagulation with heparin was given, keeping activated clotting time (ACT) at 180–220. If the patient's level of oral anticoagulation was appropriate no heparin was given (four patients). During the procedure an intensive care-certified nurse was attending, monitoring up to two simultaneously treated UF patients and a senior cardiologist was available in-house for possible emergency calls.

Continuous telemetry was performed and vital signs were checked before the treatment, 10 minutes after the start of treatment, and every hour thereafter, not exceeding 8 hours of treatment. UF treatments were administered with the patient in a sitting or supine position, according to the patient's wish.

Table 1. Patient characteristics

Variable	Value
Age (years, mean ± SD)	65 ± 10
Male gender (n, %)	7 (100%)
BNP (mean ± SD)	1140.8 ± 637
LVEF (%, mean ± SD)	33 ± 13
NYHA class (mean ± SD)	2.7 ± 0.48
Hypertension (n, %)	5 (71%)
Diabetes mellitus (n, %)	4 (57%)
Ischemic etiology (n, %)	7 (100%)
Atrial fibrillation (n, %)	4 (57%)
ICD/CRTD (n, %)	6 (86%)
Beta-blockers (n, %)	7 (100%)
Aldosterone antagonist (n, %)	3 (43%)
ACE-I and/or ARB (n, %)	4 (57%)
Systolic BP (mm/Hg, mean ± SD)	120.8 ± 17.8
Creatinine (mg/dl, mean ± SD)	1.6 ± 0.32
Sodium (mEq/dl, mean ± SD)	138.3 ± 3.3
Potassium (mEq/dl, mean ± SD)	4.8 ± 0.67
Hemoglobin (g/dl, mean ± SD)	11.1 ± 1.4

BNP = brain natriuretic peptide, BP = blood pressure, NYHA = New York Heart Association class, ICD = implantable cardioverter-defibrillator, CRTD = cardiac resynchronization therapy defibrillator, LVEF = left ventricular ejection fraction, ACE-I = angiotensin-converting enyzyme inhibitor, ARB = angiotensin receptor blocker

Table 2. UF treatment, parameters before and after, for a total of 38 UF sessions

Parameter	Before (mean ± SD)	After (mean ± SD)	*P* value
BNP	1140 ± 637	1044 ± 644	0.39
SBP	120 ± 18	124 ± 14	0.13
Creatinine (mg/dl)	1.60 ± 0.27	1.62 ± 0.32	0.78
Sodium (mEq/dl)	137.8 ± 3.79	138.3 ± 3.31	0.54
Potassium (mEq/dl)	4.81 ± 0.67	4.84 ± 0.91	0.94

BNP = brain natriuretic peptide, SBP = systolic blood pressure

RESULTS

Of the 38 treatments, only 2 courses were interrupted prematurely due to technical problems: in the first an outflow cannulation vein collapsed, and in the second patient there was a clot inside the UF device. In neither case was the patient harmed. All patients reported subjective improvement after the treatments.

On average, 1982 ml fluid was removed per UF course (range 310–3240 ml during the treatment which was interrupted for technical reasons). There were no differences in blood pressure level before and after treatment; urinary output was preserved, with 380 ml per treatment on average. As demonstrated in Table 2, there were no electrolyte disturbances during the procedures, creatinine level was stable, natriuretic peptide serum level (BNP) declined slightly from the normal, 1140 at the start of the treatment to 1044 after ($P = 0.39$). Continuous variables were expressed as means ± SD, and discrete variables as numbers and percentages. Student's *t*-test was used to assess the statistical validity of continuous variables.

No significant adverse events were recorded. Specifically, no episodes of hypotension, arrhythmias, desaturation, presyncope episodes or bleeding were noted.

DISCUSSION

HF has become an epidemic in the last few decades. The prevalence of HF is increasing in Western societies, with an average

incidence as high as 3% in adults. In Israel, this translates to more than 200,000 HF patients, of whom 30% of them (i.e., > 60,000) are in NYHA III-IV, with an average 50% readmission rate at 6 months, and expenditure of approximately 500 million shekels annually, 60% of which constitutes hospitalization costs. Clearly, prevention of such rehospitalizations is imperative [10,11].

The most common reason for re-admission is fluid retention. Physical removal of edema fluid may be an appropriate therapeutic measure and may be achieved by venesection, paracenthesis or dialysis.

UF was approved for use by recent American College of Cardiologists/American Heart Association and European College of Surgeons guidelines [12,13] and its effectiveness has been evaluated in many trials. Moreover, the use of UF "in-hospital" is continuously expanding. Our study was the first attempt to extend UF treatment to the outpatient setting in Israel, focusing on safety and technical operative aspects. The main conclusion derived from our study was that the UF approach is both safe and effective, given the monitoring level we described, even when the treatment was provided on a basis of one nurse per two simultaneously treated UF patients. Of note, this strategy of outpatient UF therapy was described previously in the literature very scantily with only a few non-randomized trials including a small number of ambulatory patients undergoing UF treatments at time intervals of weeks to 1 year periods [9].

Overall, the outcome of these studies was not different from our results, but differences in follow-up and duration of the UF treatment obviate a "head-to-head" analysis. The rate of procedure-related complications in our study was zero, as compared to four complications including two deaths related to complications of UF treatment in one of these studies [9].

Interestingly, in our study we observed only a slight decline in BNP serum levels at the end of the UF sessions. We cannot say why this decline was not more prominent, but it may be due to the BNP half-life (albeit a relatively short one) together with the chronic congested clinical profile of our patients. Interestingly, elevation of NT-proBNP levels was reported after hemodialysis using a low flux dialyzer related partly to hemoconcentration [14].

Several study limitations should be noted. The number of treated patients was small although the total number of sessions was high. Since we performed a feasibility study to evaluate UF therapy in "real life," we did not specify a strict definition for "diuretic resistance," but rather left the referral to the discretion of the HF cardiologists and treating physicians.

CONCLUSIONS

Ultrafiltration therapy is a valid option for treating ambulatory chronic heart failure patients with fluid overload. We believe that in Israel this therapy may be added to the regular medical treatment of HF but should be administered at specific heart failure centers that have the professional capability to provide this therapy safely.

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"I took a speed reading course and read *War and Peace* in twenty minutes. It involves Russia"

Woody Allen (born 1935), American actor, comedian and filmmaker. As a comic, he developed the persona of an insecure, intellectual, fretful nebbish, which he maintains is quite different from his real-life personality. He has been ranked in fourth place on a list of the 100 greatest stand-up comics. As a filmmaker he has won numerous awards