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COMPARISON OF THE SAFETY AND EFFICACY OF EARLY ULTRAFILTRATION WITH STANDARD INTRAVENOUS DIURETIC THERAPY IN PATIENTS WITH DECOMPENSATED HEART FAILURE AND VOLUME OVERLOAD

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Objective: This study was designed to compare the safety and efficacy of early ultrafiltration with standard intravenous diuretic therapy in patients with decompensated heart failure and volume overload.

Study design: Prospective, randomized, comparative study.

Place and duration of study: Karachi Institute of Heart Diseases, Karachi, Pakistan. From June 2009 to December 2009.

Methods: Patients hospitalized for heart failure with greater than two signs of hypervolemia were randomized to ultrafiltration or intravenous diuretics. Primary end points were weight loss and dyspnea assessment at 48 hours after randomization. Secondary end points included net fluid loss at 48 hours, improvement in functional class at 30 days. Safety end points included changes in renal function, electrolytes, and blood pressure.

Results: Total 18 patients were randomized to ultrafiltration or intravenous diuretics (10 in ultrafiltration group and 8 in intravenous diuretics group). At 48 hours, weight (2.8 +/- 0.15 kg vs. 1 +/- 0.23 kg) and net fluid loss (3103 ml vs. 1200 ml) were greater in ultrafiltration group. 60% of patients in ultrafiltration group were in NYHA class I at 48 hours and 80% at 30 days. While in intravenous diuretics' group 25% of patients were in NYHA Class I, 10% in NYHA Class II and 65% in NYHA class III at 48 hours and on 30 days 75% of patients were in class III and 25% were in class II.

Conclusions: In decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics. The procedure is safe as no significant side effects were noted.

Keywords: Heart Failure, Ultrafiltration, Diuretics.

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INTRODUCTION

Heart Failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive activation of neuroendocrine system leading to circulatory insufficiency and congestion. In the United States 90% of the one million annual hospitalizations for heart failure are due to volume overload[1,2].

Most patients hospitalized for decompensated heart failure show signs and symptoms of volume overload primarily due to an abnormal hemodynamic and neurohormonal status[3,4].

The morbidity of decompensated heart failure is due to volume overload, guidelines for treatment of heart failure recommends at achieving euvolumia. Standard therapy for decompensated heart failure consists predominantly of intravenous loop diuretics and vasodilators. Recently there is increasing concern regarding the safety and efficacy of diuretic based treatment strategies[5]. Diuretic resistance is common and contributes to variable inter and intra individual response[6]. They also adversely affect the hemodynamics and stimulate the Renin Angiotensin Aldosterone systems[7]. Currently all over the world increasing evidence suggest that ultrafiltration, a mechanical strategy to reduce the volume overload can be an effective alternative first line treatment strategy in patients with acute heart failure[8].

Ultrafiltration has gained increasing attention over the past few years[9], because it has shown to reduce the rate and length of rehospitalizations, very efficient in rapid extraction of fluid, and does not lead to activation of neuroharmonal axis that is thought to be the major concern for diuretic induced adverse effects[7].

Ultrafiltration involves a convective transfer of water and solutes. Plasma water is forced across a semipermeable membrane that allows the movement of water and solutes across the filter based on the transmembranous pressure difference between the blood and the filtrate side of the filter. This hydrostatic pressure applied to blood across a semipermeable membrane separates the isotonic plasma water from blood[6]. Because the solutes in blood moves freely across the semipermeable membrane, large amount of fluid can be removed without affecting serum electrolytes and other solute balance. The amount of water and solute clearance is proportional to the amount of ultrafiltrate formed. This can be manipulated by changing the pressure difference i.e. by increasing the blood flow or by applying suction to the filtrate side[10].

This is the first study using ultrafiltration in Pakistani population. We have conducted this study at our centre to assess the comparative safety and efficacy of ultrafiltration in patients with decompensated heart failure and volume overload.

METHODS

It was a prospective randomized trial conducted at Karachi Institute of Heart Disease from June 2009 to December 2009.Study was approved by hospital's ethical committee and written informed consent were obtained by all patients.

Patients above 18 years of age of both genders admitted with acute heart failure were included. They were randomized within 24 hours of hospitalization, if they have hypervolumia by at least 2 of the following criteria.

- Paroxysmal nocturnal dyspnea or orthopnea
- Peripheral edema > 2
- Jugular venous distension >7 cm
- Enlarged liver or ascites or pulmonary rales
- Radiographic pulmonary edema or pleural effusion.

By study design, there was no ejection fraction criterion.

Patients were excluded if they have one of the following:

- Acute coronary syndrome
- Serum Creatinine > 3 mg/dl
- Systolic blood pressure </= 90 mmHg
- Hematocrit < 45%
- Unattainable venous access
- Requirement of inotropic support
- Use of vasoactive drugs during the

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hospitalization before randomization
Use of iodinated contrast material
Contraindication to anticoagulation
Systemic infection.

Patients were randomized to ultrafiltration arm and standard care arm. All the patients received daily 2 gm salt restriction and 2 liter fluid intake restriction. ACE inhibitors, ARB's and beta blockers were continued by all patients as per requirement. For patients in ultrafiltration arm central or peripheral access was obtained for ultrafiltration. Duration and rate of fluid removal (up to 500 ml/hour) was decided by treating physician. Cardiosmart ultrafiltration machine was used for ultrafiltration. Ultrafiltration device consist of 0.12 m^2 polysulphone filter with adjustable flow rate (10-40 ml). Anticoagulation with heparin was recommended for all patients in ultrafiltration arm.

Patients randomized to standard care arm were treated with intravenous diuretics as bolus. Dose adjusted according to patients' response and in first 24 hours atleast twice the before hospitalization daily oral dose.

Patients were assessed at 24, 48 hours and at 30 days post randomization for net weight loss and improvement in functional class. Weight was measured in kilograms using appropriately calibrated scales at randomization, daily during hospitalization, at discharge and at days 30 on followup. Weight loss is the difference between randomization weight and the weight recorded at subsequent evaluations. Total fluid intake and output (ultrafiltrate and urine) measured during the first 48 hours after randomization were used to calculate net fluid losses.

New York Heart Association Classification (NYHA) was used for assessment of functional status at randomization and subsequently. Physical examination, vital signs, complete blood count and chemistries were done at randomization and 24 hours, 48 hours and at 30 days after randomization.

The primary efficacy endpoints were weight loss and functional status assessment at 48 hours after randomization. The primary safety end points were as follows:

Changes in blood pressure (episodes of hypertension requiring intervention) at 24 and 48 hours post randomization.

Changes in serum creatinine, blood urea nitrogen, electrolytes and hemoglobin at 24, 48 hours and 30 days post randomization.

The secondary efficacy endpoint were
Net fluid loss at 48 hours

Improvement in functional status at 30 days.

Statistical analysis: Due to very small sample size descriptive method was used for statistical analysis. Percentages and mean +/- standard deviations were used for comparision of two groups.

RESULTS

Total 18 patients were randomized to ultrafiltration or standard therapy group (10 in ultrafiltration group and 8 in standard therapy group).

Baseline demographics and comorbidities were same in both groups (Table 1), as also functional status and vital signs at randomization (Table 2) and heart failure characteristics (Table 3).

In ultrafiltration group, fluid was removed at an average rate of 200 ml/hour for 12+/- 2 hours for 48 hours post randomization.

At 48 hours, weight loss was greater in ultrafiltration group as compared to standard care group (2.8 +/- 0.15 kg vs 1+/- 0.23 kg). 60% of patients in ultrafiltration group were in NYHA Class I at 48 hours. While in standard care group

Table 1: Base line Demographics and Comorbidities

Characteristics	Ultrafiltration Arm N=10	Standard Care Arm N=8
Age	50.5+/-12.39	60.87+/-13.45
Gender (Male %, Female %)	90, 10	80, 20
HTN	70%	72.2%
DM	20%	27.3%
IHD	30%	18.2%
CMP	30%	36.5%
Valvular Heart Disease	10%	10%
Prior MI	20%	27.3%
PCI	20%	27.3%
CABG	20%	27.3%

Table 2: Baseline Functional capacity and Vital Signs

Characteristics	Ultrafiltration Arm N=10	Standard Care Arm N=8
NYHA Class III % IV%	 60 40	 45.5 54.6
Weight (kg)	71.90 +/- 13.94	67.25+/-9.66
Systolic BP (mm Hg)	112.50+/-17.19	114.50+/-23.21
Heart rate (bpm)	76.80 +/-6.81	82.24+/-6.96

25% of patients were in NYHA class I, 10% in NYHA Class II and 65% in NYHA Class III at 48 hours.

No clinically significant changes in serum biochemistries and hematocrit noted in both groups. No episode of hypotension requiring vasopressor was noted in both groups at 48 hours after randomization.

At 48 hours net fluid loss was greater in ultrafiltration group then standard care group (3103 ml VS 1200 ml)

At 30 days, in ultrafiltration group 80% of patients were in NYHA Class I, 10% in NYHA class II and 10% in NYHA Class III. While in standard care group 75% of patients were in class III and 25% were in Class II.

Table 3: Baseline Heart Failure Characteristics

Characteristics	Ultrafiltration Arm N= 10	Standard Care Arm N=8
Prior Heart failure %	70	75
% of patients with LVEF <40%	65	60
S 3 %	70	72.2
JVP >10 cm %	100	72.2
Pulmonary Rales %	100	72.2
Peripheral edema %	100	72.2

DISCUSSION

The study has demonstrated that ultrafiltration is safe, effective and simple method for early and long term symptomatic improvement in patients with acute decompensated heart failure. This was a small study performed first time in Pakistan but our results are comparable to international studies conducted with larger number of patients.

Marenzi et al studied the effects of ultrafiltration in 24 patients with refractory heart failure[11]. Ultrafiltration resulted in 4.9 L of fluid removal over a period of 9 hours. This and other uncontrolled studies of ultrafiltration in heart failure[12-14] showed that ultrafiltration could be performed safely and could result in significant volume removal and symptom relief.

In UNLOAD (Ultrafiltration Vs Intravenous diuretics for patients hospitalized for acute decompensated HF) at 48 hours, weight (5+/- 3.1 vs. 3.1 +/- 3.5 Kg; p=0.001) and net fluid loss (4.6 vs. 3.3 L; p= 0.001) was greater in ultrafiltration group[15]. Two studies which were conducted in 2005 Rapid- CHF trial[2] and Euphoria trial[16] also proves that ultrafiltration is superior to diuretic therapy in salt and water removal. Early ultrafiltration in patients with fluid overload and diuretic resistance allow early discharge of patients and there is no clinical justification to delay ultrafiltration. Improved 30 day NYHA class in ultrafiltration group suggested a link between volume reduction during hospitalization and subsequent functional class. A possible explanation for that is ultrafiltration removes more total body sodium resulting in more decrease in total body volume compared to diuretics as sodium is the major determinant of extracellular fluid volume. Urine produced by loop diuretics is hypotonic compared to plasma, whereas ultrafiltrate is isoosmotic and isonatremic.

Several investigators[18-24] have now reported the usefulness of ultrafiltration in various subsets of patients with decompesated heart failure. Further studies suggest that wearable technologies might become available soon to treat patients in ambulatory and de-hospitalized settings. These new technologies may help to cope with the increasing demand for care of decompensated heart failure patients.

Study Limitations:

The sample size is very small and treatment targets in both groups were not prespecified, rate and duration of fluid removal was also not specified in study protocol.

CONCLUSION

Early Ultrafiltration produces greater weight loss as compared to intravenous diuretics without compromising the hemodynamic status and renal

parameters of patients. It is a safe and effective procedure. The cost effectiveness of ultrafiltration is not yet established but it may have long term favorable economic implications by decreasing the duration of hospital stay and rehospitalization. Study with larger number of patients is required to further look into this matter.

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