Diuretics and Ultrafiltration in Acute Heart Failure Syndrome

A Meta-Analysis

Qi ZHI,¹ MM and Jiang Chang LIANG,² MM

SUMMARY

The use of diuretics and ultrafiltration in acute heart failure syndrome (AHFS) has been investigated in a number of randomized controlled trials (RCTs). However, the benefits have been variable. We therefore performed a meta-analysis to examine the overall effect of all-cause mortality, rehospitalization, renal function, dyspnea relief, and adverse events in patients with AHFS. We identified RCTs by a systematic search of MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials Register Database. Eligible RCTs were those that enrolled patients with AHFS and involved comparison of diuretic versus ultrafiltration therapy. Five RCTs with a total of nearly 500 patients were included. Overall, ultrafiltration therapy was not associated with significantly decreased risk of all-cause mortality (relative risk [RR], 0.977; 95% confidence interval [CI], 0.602 to 1.587; $P = 0.925$; $I^2 = 0.0\%$), rehospitalization (RR, 0.903; 95% CI, 0.696 to 1.170; $P = 0.440$; $I^2 = 77.4\%$), dyspnea score (weighted mean difference [WMD], 0.168; 95% CI, -0.318 to 0.653; $P = 0.498$; $I^2 = 11.4\%$) and creatinine (WMD, 0.055 mg/mL; 95% CI, -0.101 to 0.210; $P = 0.491$; $I^2 = 48.4\%$). However, there was significantly more weight loss (WMD, 1.333 kg; 95% CI, 0.186 to 2.479; $P = 0.023$; $I^2 = 57.7\%$) and net fluid removal (WMD, 1459.432 mL; 95% CI, 275.911 to 2642.953; $P = 0.016$; $I^2 = 25.2\%$) in the ultrafiltration-therapy group. There was no significant difference in the risk of adverse events between the two groups. Compared with diuretic therapy, ultrafiltration produces greater weight loss and net fluid removal in a safe and effective manner. (Int Heart J 2013; 54: 390-394)

Key words: Renal function

Heart failure is a major and growing public health problem worldwide, and there is a pressing need to improve outcomes and decrease costs.¹⁾ Although there have been therapeutic advances in the HF drug treatment of chronic HF, the prognosis of patients with acute heart failure syndrome (AHFS) remains poor.¹⁾ Fluid retention is responsible for nearly 90% of HF hospitalizations, and intravenous loop diuretics remain the first-line therapy for AHFS.²⁾ However, the efficacy of loop diuretics is balanced by the limitations of diuretic resistance, neurohormonal activation, and worsening renal function.³⁾

Peripheral venovenous ultrafiltration represents an alternative approach in this setting. Several small studies suggest that ultrafiltration may allow for greater net fluid removal, less neurohormonal activation, and improved quality of life and reduced rehospitalization rates.⁴⁻⁶⁾ However, the CARRESS-HF trial⁷⁾ reported that diuretic-therapy was superior to ultrafiltration, so the optimal method for successful decongestion while minimizing changes in renal function and neurohormonal activation remains unclear. The aim of the present study was to evaluate the risk of all-cause mortality, rehospitalization, renal function, weight change, and adverse events by conducting a meta-analysis of RCTs of diuretic versus ultrafiltration therapy in AHFS.

METHODS

Data sources and searches strategy: We searched MEDLINE (source, PubMed, 1966-December 2012), EMBASE (1974 to December 2012), the Cochrane Controlled Clinical Trials Register Database (through December 2012), and the ClinicalTrials.gov Website (through December 2012) using the terms “diuretic”, “ultrafiltration”, “acute heart failure”, and “treatment”. Manual reference checking of the bibliographies of all relevant articles was performed. We manually searched the abstracts of annual scientific sessions of the American Heart Association (2005-2012), the European Society of Cardiology (2005-2012), the American College of Cardiology (2005-2012), the European Heart Failure Society, and the Heart Failure Society of America (through 2012). No restrictions were applied.

Study selection: We first conducted an initial screening of titles and/or abstracts. A second evaluation was based on full-text review. Trials considered eligible were those that met the following criteria: 1) the study design was a prospective RCT; 2) the study was conducted in patients with AHFS; 3) the intervention consisted of diuretic and ultrafiltration therapy; and 4) the outcomes of interest were all-cause mortality, HF rehospitalization, renal function, and weight change, and adverse events.

From the Departments of ¹ Cardiology, and ² Orthopedics, 309th Hospital of Chinese People's Liberation Army, Beijing, China.

Address for correspondence: Qi Zhi, MM, Department of Cardiology, 309th Hospital of Chinese People's Liberation Army, No. 17 Montenegro Hu Road, Haidian District, Beijing, 0086-10091 China.

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Data extraction: Data extraction was performed by two independent reviewers using a standardized data-collection form, and disagreements were resolved by discussion. The details extracted were patient characteristics, study quality, and clinical outcomes that included all-cause mortality, heart failure, and rehospitalization in both the diuretic and ultrafiltration groups.

Quality assessment: The principal components used for quality assessment were generation of random sequence, allocation concealment, blinding of outcome assessment, loss of follow-up of outcome measure, and selective outcome reporting.¹⁶⁾ Quality assessment was undertaken independently by two reviewers (Q. Z. and J.-C. L.).

Data synthesis and analysis: Results were quantitatively analyzed with STATA (version 12.0, Stata Corp, College Station, TX, USA) using the DerSimonian and Laird random-effects model⁸⁾ with 95% confidence interval (CI) on an intent-to-treat basis.

Heterogeneity was examined by the I^2 statistic and the chi-squared test, and a value of $I^2 > 50\%$ was considered as a substantial level of heterogeneity. Statistical significance was set at the 0.05 level for both the I^2 test for heterogeneity and Z-test for relative risk (RR) and weighted mean difference (WMD).

RESULTS

Search results: We initially identified 664 potentially relevant articles. Forty-one articles were considered to be of interest and were retrieved for full-text review. Thirty-six articles were excluded, and finally 5 studies were included in our meta-analysis. A flow chart showing the study selection is presented (Figure 1).

Study characteristics: The 5 published RCTs^{4,7,9-12)} in our meta-analysis had a total of 494 patients. Patients who were hospitalized with acute decompensated heart failure,⁷⁾ or with 2+ peripheral edema, higher jugular venous pressure, or pulmonary edema, or pleural effusion on chest radiography,^{4,9-11)} or with NYHA class III/IV HF symptoms¹²⁾ were eligible for enrollment, and those with acute coronary syndrome, higher serum creatinine, or higher hematocrit, or hemodynamic instability were excluded.^{4,7,9-12)} They compared ultrafiltration therapy with diuretic therapy. The total number of patients in each study ranged from 30 to 200, and the duration of follow-up varied from 96 hours to 90 days. The age of the participants ranged from 60 to 73 years. Most were men (mean, 77.8%), 61.7% patients had hypertension and 45.4% had diabetes mellitus, and the baseline BNP was 4645.5 pg/mL (Table I).

All trials used intravenous diuretics (furosemide, 160-500 mg), and CARRESS-HF used stepped pharmacologic-therapy intervention. The ultrafiltration rate of most trials was 200 mL/hour, and the primary endpoint in most trials was weight change (Table II).

Methodological quality assessment: All trials randomized the participants, but only 3^{4,7,12)} reported details of the randomization process used. These were permuted block randomization stratified according to center.^{4,7,12)} Two studies^{7,12)} used methods that concealed treatment allocation adequately. Four trials^{4,7,9,12)} blinded outcome assessors to treatment allocation. A power calculation to determine the number of patients required

Figure 1. Flow chart of trials selection. Flow chart shows the literature search for RCTs of ultrafiltration versus diuretic therapy for patients with acute heart failure syndrome. RCT indicates randomized controlled trial.

to show a difference between treatment groups on their primary outcome was undertaken in 5 trials. Loss of follow-up of the outcome measure was $< 10\%$ in most studies except one¹²⁾ (Table III).

All-cause mortality and rehospitalization: All 5 trials^{4,7,9-12)} provided data about all-cause mortality, and found that ultrafiltration therapy was not associated with significantly lower risk of all-cause mortality (RR, 0.977; 95% CI, 0.602 to 1.587; $P = 0.925$; $I^2 = 0.0\%$) compared with the ultrafiltration group (Figure 2). Three trials^{4,7,12)} found that there was no significant difference in the risk of rehospitalization between the ultrafiltration therapy group and diuretic group (RR, 0.903; 95% CI, 0.696 to 1.170; $P = 0.440$; $I^2 = 77.4\%$) (Figure 3).

Renal function, dyspnea, net fluid, and weight loss: Four studies^{7,9,11,12)} presented renal function data and reported there was no significant increase in the creatinine level in the ultrafiltration-therapy group (WMD, 0.055; 95% CI, -0.101 to 0.210; $P = 0.491$; $I^2 = 48.4\%$) (Figure 4). Also, there was no significant difference in the dyspnea score^{4,7,11)} between the two groups (WMD, 0.168; 95% CI, -0.318 to 0.653; $P = 0.498$; $I^2 = 11.4\%$). However, 3 trials found that ultrafiltration therapy was associated with significantly greater weight loss^{4,7,11)} and net fluid removal^{4,7,12)} (WMD, 1.333; 95% CI, 0.186 to 2.479; $P = 0.023$; $I^2 = 57.7\%$ and WMD, 1459.432; 95% CI, 275.911 to 2642.953; $P = 0.016$; $I^2 = 25.2\%$) (Figure 5).

Adverse events: Three studies^{4,7,12)} provided data on adverse events, and ultrafiltration was not associated with significant decreased risk of emergency visit (RR, 1.666; 95% CI, 0.330 to 8.401; $P = 0.536$; $I^2 = 92.0\%$) (Figure 6) or worsening of heart

Table I. Characteristics of Individual Trials in This Review

RCT	Year	FU,	Patients, No.	Age, years	Male, %	LVEF, %	HT, %	DM, %	HF, %	BNP, pg/mL
RAPID-CHF ⁹⁾	2005	48h	40	67.5 [§]	70.0	69.0 [‡]	60.0	35.0	NR	NR
UNLOAD ^{4,10)}	2007	90d	200	63.0	70.0	71.0 [‡]	74.0	50.0	95.0	1256
ULTRADISCO ¹¹⁾	2011	96h	30	72.4	87.0	34.0	60.0	40.0	100.0	5063 [‡]
Hanna ¹²⁾	2012	90d	46	60.0	84.2	19.0	52.9	36.8	NR	8256 [‡]
CARRESS-HF ⁷⁾	2012	60d	188	69.0	78.0	30.0	NR	65.0	75.0	4007 [§]

Values are *n* (%) or mean. FU indicates follow-up; LVEF, left ventricular ejection fraction; HT, hypertension; DM, diabetes mellitus; HF, heart failure; BNP, B-type natriuretic peptide, NR, not reported; [§], median; [‡], LVEF < 40%; and [‡], NT-proBNP.

Table II. Interventions and Primary Endpoint of RCTs

First Author and/or RCT (Ref.#)	Year	Diuretic dosing	Ultrafiltration	Primary endpoint
RAPID-CHF ⁹⁾	2005	Median daily dose of furosemide, 160 mg	Single 8-hour session, with most sessions removing 3-4 L	Weight loss at 24 hours
UNLOAD ^{4,10)}	2007	Average daily dose of furosemide, 181 mg	Average UFR, 241 mL/hour, average UF duration, 12.3 hours	Weight loss and dyspnea assessment at 48 hours
ULTRADISCO ¹¹⁾	2011	Continuous infusion of furosemide, 250-500mg/dL, urine output > 2L/dL	UFR, 100-300 mL/hour, median duration 46 (IQR, 39-71) hours	Change of clinical, biochemical and hemodynamic variables at 36 hours
Hanna ¹²⁾	2012	Dosing at discretion of physician (dose NR)	UF started at 400 mL/hour × 6 hours, then decreased to 200 mL/hour, mean UFR, 272 mL/hour	Time required for the PCWP to be maintained at ≤ 18 mmHg
CARRESS-HF ⁷⁾	2012	Stepped algorithm of furosemide and metolazone, daily urine output of 3-5 L	UFR, 200 mL/hour, median duration, 40 (IQR, 28-67) hours	Change in the serum creatinine and weight at 96 hours

IQR indicates interquartile range; NR, not reported, PCWP, pulmonary capillary wedge pressure; UF, ultrafiltration; and UFR, ultrafiltration rate.

Table III. Methodological Quality Assessment

First Author and/or RCT (Ref.#)	Year	Generation of randomized sequence	Concealment of allocation	ITT	Blinding of outcome assessors	Loss of follow-up (%)
RAPID-CHF ⁹⁾	2005	B	B	Y	B	0
UNLOAD ^{4,10)}	2007	A	B	Y	B	0
ULTRADISCO ¹¹⁾	2011	B	B	B	B	0
Hanna ¹²⁾	2012	A	A	Y	B	19
CARRESS-HF ⁷⁾	2012	A	A	Y	A	0

A indicates adequate; B, unclear or not reported in the published data; C, inadequate; Y, yes; RCT, randomized controlled trial; and ITT, intent-to-treat.

failure (RR, 0.726; 95% CI, 0.422 to 1.248; $P = 0.247$; $I^2 = 68.9\%$).

DISCUSSION

Our review is the first meta-analysis comparing ultrafiltration therapy and diuretic therapy for patients with AHFS. Moreover, we have provided evidence that ultrafiltration therapy can produce greater weight loss and net fluid removal in a safe and effective manner.

Since the RAPID-CHF (Relief for Acutely Fluid Overload Patients with Decompensated Congestive Heart Failure) study was published nearly 10 years ago suggesting ultrafiltration therapy can significantly improve dyspnea and remove fluid⁹⁾ at 48 hours, several other trials including UNLOAD, ULTRADISCO and the CARRESS-HF^{4,7,10,11)} have explored the concept. The UNLOAD trial⁴⁾ randomized 200 patients with AHFS to either UF or loop diuretic therapy and found that

UF is associated with significantly greater weight loss (5.0 ± 3.1 kg versus 3.1 ± 3.5 kg; $P = 0.001$). However, there were concerns about whether diuretics were used optimally, which patients should have received ultrafiltration, and how ultrafiltration should be performed.³⁾ In the CARRESS-HF trial, there was no significant difference in weight loss at 96 hours (5.7 ± 3.9 kg versus 5.5 ± 5.1 kg; $P = 0.58$) and 60-day follow-up between the 2 groups owing to the stepped pharmacologic therapy involving increasing doses of loop diuretics (with or without metolazone), vasodilators, and/or inotropes, and the diuretic dose was higher than other trials.⁷⁾ We found that ultrafiltration therapy was associated with significantly greater weight loss (1.333 kg; 95% CI, 0.186 to 2.479; $P = 0.023$) and net fluid removal (1459.432 mL; 95% CI, 275.911 to 2642.953; $P = 0.016$).

Declining kidney function during therapy of the congested state (cardiorenal syndrome type I) is one of the strongest predictors of short- and long-term adverse events,¹³⁾ and twice (14.4% versus 7.7%; $P = 0.528$) as many patients in the ultra-

Figure 2. All-cause mortality meta-analysis of 4 trials. Random-effect model ($I^2 = 0.0\%$; $P = 0.860$). CI indicates confidence interval.

Figure 3. HF rehospitalization meta-analysis of 3 trials. Random-effect model ($I^2 = 66.8\%$; $P = 0.049$). CI indicates confidence interval.

Figure 4. Serum creatinine level meta-analysis of 4 trials. Random-effect model ($I^2 = 48.4\%$; $P = 0.121$). CI indicates confidence interval.

Figure 5. Net fluid removal meta-analysis of 3 trials. Random-effect model ($I^2 = 65.2\%$; $P = 0.057$). CI indicates confidence interval.

Figure 6. Emergency visits meta-analysis of 3 trials. Random-effect model ($I^2 = 92.0\%$; $P = 0.000$). CI indicates confidence interval.

filtration group experienced an increase in serum creatinine level > 0.3 mg/dL during the first 24 hours of treatment^{4,10} in the UNLOAD study, so there is controversy about the effect of ultrafiltration and high-dose furosemide therapy on renal function. CARRESS-HF is the only trial to report a significantly increased incidence of worsening kidney function in the ultrafiltration arm compared to the diuretic group ($+0.23 \pm 0.70$ mg/dL versus -0.04 ± 0.53 mg/dL; $P = 0.003$) at 96 hours follow-up. However, Patarroyo¹⁴ found that there was no significant difference in serum creatinine level (2.2 ± 0.9 mg/dL versus 2.4 ± 1 mg/dL; $P = 0.12$) when the ultrafiltration therapy duration proceeded for 48 hours. Meanwhile, in the DOSE trial, a higher proportion of patients in the high-dose furosemide group (2.5 times the previous oral dose) experienced an increase in serum creatinine level > 0.3 mg/dL during the first 72 hours of therapy (23% versus 14%; $P = 0.04$).¹⁵ Pooling 5 RCTs, we concluded that ultrafiltration therapy is not associated with a significant increase in the creatinine level (0.055 mg/dL; 95% CI, -0.101 to 0.210; $P = 0.491$).

In the UNLOAD trial,^{4,10} the incidences of HF rehospitalization and ER visits at 90 days were significantly lower in the ultrafiltration therapy group (18% versus 32%, $P = 0.037$ and 21% versus 44%, $P = 0.009$). However, Bart⁷ found that there were no differences in HF hospitalization (26% versus 26%, $P = 0.97$), any-cause hospitalization (51% versus 40%, $P = 0.12$) and ER visits (21% versus 14%, $P = 0.21$) between the ultrafiltration therapy and diuretic therapy groups. In the end, we concluded that ultrafiltration therapy is not associated with higher risks of all-cause mortality, rehospitalization, and adverse events including ER visits and HF worsening.

Study limitations: Given the lack of individual data in each study, we did not adjust our analyses for compliance to assigned ultrafiltration therapy. Also, our results are subject to limitations inherent to any meta-analysis based on pooling of data from different studies with different designs, targets, and follow-ups. Based on the findings of our meta-analysis, future studies will require a large number of patients and careful matching of diuretic and ultrafiltration strategy, endpoints, and other key clinical variables to definitively address the true effectiveness of ultrafiltration treatment in the treatment of AHFS.

Conclusions: In summary, our study suggests that ultrafiltration therapy can significantly produce more weight loss and net fluid removal in a safe and effective manner.

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