Meta-Analysis of Ultrafiltration versus Diuretics Treatment Option for Overload Volume Reduction in Patients with Acute Decompensated Heart Failure

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Abstract

Introduction: Although diuretics are mainly used for the treatment of acute decompensated heart failure (ADHF), inadequate responses and complications have led to the use of extracorporeal ultrafiltration (UF) as an alternative strategy for reducing volume overloads in patients with ADHF.

Objective: The aim of our study is to perform meta-analysis of the results obtained from studies on extracorporeal venous ultrafiltration and compare them with those of standard diuretic treatment for overload volume reduction in acute decompensated heart failure.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases were systematically searched using a pre-specified criterion. Pooled estimates of outcomes after 48 h (weight change, serum creatinine level, and all-cause mortality) were computed using random effect models. Pooled weighted mean differences were calculated for weight loss and change in creatinine level, whereas a pooled risk ratio was used for the analysis of binary all-cause mortality outcome.

Results: A total of nine studies, involving 613 patients, met the eligibility criteria. The mean weight loss in patients who underwent UF therapy was 1.78 kg [95% Confidence Interval (CI): −2.65 to −0.91 kg; p < 0.001) more than those who received standard diuretic therapy. The post-intervention creatinine level, however, was not significantly different (mean change = −0.25 mg/dL; 95% CI: −0.56 to 0.06 mg/dL; p = 0.112). The risk of all-cause mortality persisted in patients treated with UF compared with patients treated with standard diuretics (Pooled RR = 1.00; 95% CI: 0.64–1.56; p = 0.993).

Conclusion: Compared with standard diuretic therapy, UF treatment for overload volume reduction in individuals suffering from ADHF, resulted in significant reduction of body weight within 48 h. However, no significant decrease of serum creatinine level or reduction of all-cause mortality was observed. (Arq Bras Cardiol. 2015; 104(5):417-425)

Keywords: Heart Failure / therapy; Hemofiltration; Ultrafiltration; Diuretics.

Introduction

Acute decompensated heart failure (ADHF) is one of the leading causes of hospitalization in the U.S. A vast majority of these patients admitted to the hospital has to be treated for volume overload[1,2]. Volume overload is frequently associated with poor prognosis in heart failure (HF) patients; therefore, current medical guidelines recommend non-pharmacological and pharmacological interventions to treat volume overload[3,4].

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Therapeutically for reducing overload volume, ADHD patients are treated with diuretics administered intravenously[3,5]. However, chronic use of diuretics has been associated with negative neuro-hormonal effects[7] and may cause diuretic resistance.[6] Diuretic resistance is associated with poor prognosis and higher incidence of morbidity in HF patients[8].

Extracorporeal Venous Ultrafiltration (UF)—an invasive procedure—may be used as an effective alternative approach to reduce volume overload in patients resistant to conventional diuretics[9-12]. However, the benefits of UF therapy is not very clear. In a randomized trial conducted recently, UF failed to produce better efficacy than that produced by diuretics and was also associated with an increased rate of adverse events[13]. In contrast, our recent findings form meta-analysis data by incorporating the results of one recent study suggested that UF may be effective in

reducing volume overload, however we have not considered results from some studies reported very recently[14].

Therefore, in this present study, we seek to evaluate and compare the study results obtained using UF and intravenous diuretics as treatment options for treating ADHF. Our primary objective is to compare weights and measure changes in creatinine level in patients who were undergoing treatment with UF or diuretics. Our secondary objective is to evaluate any potential differences in all-cause mortality rates.

Methods

Following a pre-specified protocol, we systematically searched the databases of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials; we started from the beginning of each database and collected data till May 8th, 2013. The search strategy included all manuscripts published in English. Keywords used for searching were "ultrafiltration," "heart failure," and "clinical trials." The retrieved references were manually searched for relevant publications and references from the included publications were further searched for potential relevant studies. Two reviewers independently evaluated and retrieved articles using pre-specified criteria (EB, MSB). Disagreements were resolved by consensus. The reasons for exclusions were systematically logged (Figure 1). Our approach strictly adheres to the guidelines set forth by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15].

Eligibility criteria

Studies in all languages were considered eligible if it would meet the following criteria: 1) prospective 2) included hospitalized patients over 18 years of age with clinical evidence of acute ADHF; the clinical characteristics of ADHF included the presence of orthopnea or paroxysmal nocturnal dyspnea [PND], jugular venous pressure [JVP] > 10 cm Hg, pulmonary edema or effusion on chest X-ray, left ventricular end diastolic pressure > 20 mm Hg, ascites, presacral, and edema or the patient have met the criteria set forth by New York Heart Association Heart Failure classification III or IV during hospital admission or have displayed cardio renal syndrome requiring hospitalization 3) UF therapy was initiated within 48 hours of hospitalization 4) UF intervention was compared with the standard intravenous or oral diuretic therapy 5) reported primary weight loss, change in serum creatinine level and all-cause mortality as primary outcomes during the study period. We excluded studies related to non-human subjects, studies without a control group, and studies in which UF was performed as an adjunctive therapy.

Data Extraction

Two authors (CKS and JO) independently extracted data from each study included in the analysis and all discrepancies were resolved by consensus. The extracted data included the year of publication, study country, inclusion and exclusion criteria, patient demographics for both groups (the number of individuals in each group, age, race, gender, and co-morbidities at baseline), quality indicators (details of randomization, data analysis, and sample size calculations), average weight (expressed in kilogram) at the start and end of the study period, average change in weight (when both values were not available), average measured creatinine level (expressed in mg/dL) at baseline along with follow up, average change in creatinine level (when both values were not available), and death.

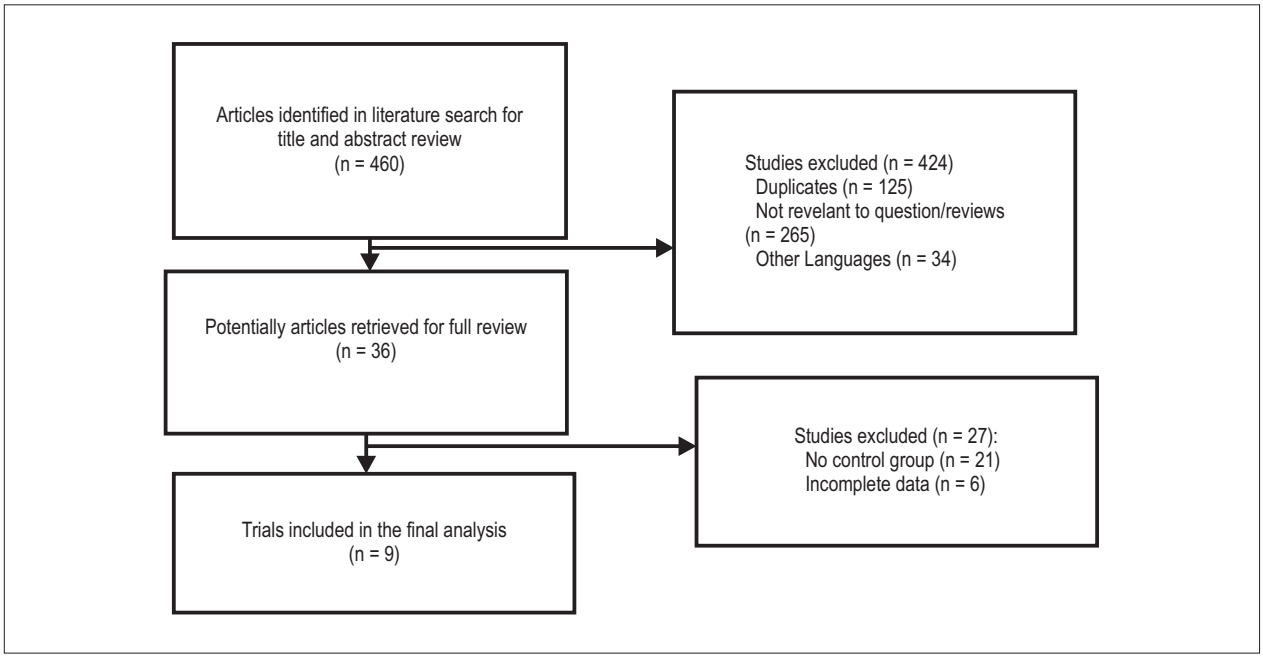

Figure 1 – *QUORUM flow diagram detailing the process of determining eligible randomized control trials (RCTs) for inclusion in meta-analysis.*

Statistical Analysis

Pooled estimates for the outcomes—weight change, change in creatinine level, and the risk for all-cause mortality were computed using random effect models of Der Simonian and Laird[16]. Pooled weighted mean differences (WMD) were calculated for weight loss and change in creatinine level whereas a pooled risk ratio was derived for binary mortality. Heterogeneity across studies was assessed using the Q-test and I^2 statistics[17]. Publication bias was evaluated statistically using the Egger's and Begg's tests and visually using Egger's plots[18].

We performed sensitivity analysis by systematically excluding each study sequentially to assess trends in study estimates of each individual study that contributed to the pooled estimates during the study period. Stratified analysis was performed to account for heterogeneity for the outcomes related to weight loss and change in creatinine level. We also performed additional stratified analyses on treatment intention versus per protocol analysis, randomized versus non-randomized studies, and larger versus smaller sample size. For performing stratified analyses, we have considered the following risk factors: diabetes, coronary artery disease at baseline, age, gender, and the concentration of B-type natriuretic peptide (BNP). We divided the study results into two groups based on the median value indicating the prevalence of the risk factors, and further evaluated the heterogeneity within groups. The studies were further stratified according to median values obtained for creatinine levels for examining heterogeneity in the outcome related to weight change. Similar stratification was implemented for examining heterogeneity in measuring changes of creatinine levels by using the median values obtained for weight change measurements. All statistical analyses were performed using Stata version 12 (College Station, TX). We used $\alpha = 0.05$ for analyzing significant differences between different treatment groups with regard to meta-relative risks (mRR) and WMD.

Results

Description of Studies

Nine studies met our inclusion and exclusion criteria and were incorporated in this meta-analysis (Table 1)[19-21]. Of all eligible studies that met our predefined search criterion (n = 36), 21 were excluded because they lacked a control group and six were excluded due to incomplete data (Figure 1). One study[22] had overlapping patient population with a larger trial[23], and its data were only used when information was not reported in the larger study. The primary outcomes—change in weight and the change in creatinine level starting from baseline values were reported in seven studies. The secondary outcome—all-cause mortality was reported in six studies. A total of 613 patients were included; the control group consisting of 306 patients and the UF group consisting of 307 patients.

All studies were published during the year 2005 or later. Eight out of nine studies were related to clinical trials, and only one was a retrospective observational study. Of the six randomized studies selected, three studies were prospective clinical trials with an intention to treat analysis. The eligible trials were not blinded and treatment allocation concealment methods were not used. Three studies reported using the Aquadex system for ultrafiltration and one study used PRISMA system for ultrafiltration. The remaining studies did not mention the device used for ultrafiltration. Furthermore, sample size calculation was performed in three studies. Quality assessments of the selected studies are presented in (Table 2).

The mean age of patients ranged from 43 to 70 years in the control arm and from 52 to 72 years in the intervention arm. The majority of patients in both treatment groups were men (range 60% to 88% for control arm, range 70% to 88% for UF arm) and caucasian (range 30%–94% for control arm, range 55%–77% for UF arm). The incidence of diabetes varied across studies ranging from 29% to 67% among control patients and 30% to 78% among UF patients (Table 1).

Meta-Analysis and Assessment of Bias

In the pooled analysis, significant increase in weight loss was observed between the two groups after 48 hours of treatment [1.78 kg difference; 95% Confidence Interval (CI): −2.65 to −0.91 kg; $p < 0.001$] (Figure 2A). However, post-intervention reduction in creatinine level failed to demonstrate a significant difference between the two groups (0.25 mg/dL; 95% CI: 0.56–0.06 mg/dL; $p = 0.112$) (Figure 2B). Finally, no significant difference was observed for all-cause mortality in patients treated with UF compared with those treated with diuretics (Pooled RR = 1.00; 95% CI: 0.64–1.56; $p = 0.99$) (Figure 2C).

There was evidence of heterogeneity with respect to weight change (Q-test $p = 0.006$; $I^2 = 64\%$) and change in creatinine level (Q-test $p = 0.0003$; $I^2 = 76\%$), but not for all-cause mortality (Q-test $p = 0.827$; $I^2 = 0$). Additionally, we found no evidence of publication bias among weight loss estimates (Egger's test $p = 0.09$; Begg's test $p = 0.45$). However, there was visual evidence of publication bias based on symmetrical distribution of study estimates on the funnel plot (Figure 3A). While there was no statistical evidence of publication bias for change in creatinine levels (Egger's test $p = 0.083$, Begg's test $p = 0.453$), visual inspection revealed asymmetric distribution of study estimates (Figures 3B). This was also true for all-cause mortality outcomes (Egger's test $p = 0.083$, Begg's test $p = 0.453$) (Figure 3C).

Stratified Analysis

The results remained heterogeneous for weight change outcomes upon stratification by gender, age, diabetes, coronary artery disease (CAD), and creatinine level. After stratification by BNP, only studies corresponding to higher values of BNP remained heterogeneous. Studies with lower BNP values showed significant reduction in weight without notable heterogeneity. Similar findings were noted for studies where BNP values were not reported (Figure 4).

When stratified by intention-to-treat versus per-protocol analysis, the intention-to-treat studies demonstrated no benefit with regard to weight reduction with significant heterogeneity ($p = 0.001$) (Figure 5A). In addition, the per-protocol studies demonstrated significant weight reduction with virtually no

Table 1 – Demographic characteristics of the studies included in the meta-analysis

First author	Bart	Costanzo	Libetta	Bartone	Rogers	Giglioli	Bart	Badawy	Hanna
Year	2005	2007	2007	2008	2008	2011	2012	2012	2012
Journal	JACC	JACC	NDT	CHF	JCF	EJHF	NEJM	JCC	CHF
country	USA	USA	Italy	USA	USA	Italy	USA	Egypt	USA
Trial	RAPID-CHF	UNLOAD	-	-	UNLOAD	ULTRADISCO	CARESS-HF	Un-named	Un-named
Sample size	40	200	10	50	19	30	188	40	36
Age - Control	69.5	63 ± 14	43.3 ± 11.6	66.8 ± 14.3	64 ± 15	65.8 ± 18.4	66	62 ± 14	59 ± 15.5
Age - UF	67.5	62 ± 15	51.5 ± 9.4	66.6 ± 14.4	54 ± 16	72.4 ± 14.1	69	64 ± 11	60 ± 9.1
Male (%) - Control	70%	70%	NA	68%	60%	87%	72%	60%	76%
Male (%) – UF	70%	68%	NA	68%	78%	87%	78%	80%	85%
White race control	NA	52%	NA	NA	30%	NA	71%	NA	94%
White race UF	NA	55%	NA	NA	56%	NA	77%	NA	73%
Diabetes control (%)	53%	49%	NA	52%	50%	60%	67%	55%	29%
Diabetes UF (%)	30%	5%	NA	68%	78%	40%	65%	60%	37%
CAD (%) control	30%	48%	NA	60%	60%	60%	51%	65%	29%
CAD (%) UF	30%	56%	NA	76%	78%	60%	70%	60%	21%
Weight loss control (Kg)	1.9 ± 1.2	3.1±3.5	NA	2.9 ± 3.4	1.9 ± 2.2	6.9 ± 1.8	5.5 ± 5.1	3.7 ± 3.2	1.0 ± 2.5
Weight loss UF (Kg)	2.5 ± 1.2	5 ± 3.1	NA	7.1 ± 6.2	2.7 ± 2.6	9.1 ± 1.7	5.7 ± 3.9	6.3 ± 3.5	4.7 ± 3.5
Creatinine control at baseline	1.8	1.5 ± 0.5	1.2 ± 0.5	1.8 ± 0.8	1.6 ± 0.8	1.9 ± 0.6	2.1	1.4 ± 0.7	1.7 ± 0.8
Creatinine UF at baseline	1.6	1.5 ± 0.5	1.9 ± 1.6	1.9 ± 0.8	1.8 ± 0.8	2.2 ± 0.8	1.9	1.4 ± 0.8	1.6 ± 0.7
Change in creatinine control	0.1		0.0 ± 0.41	0.1 ± 1.65	0.11 ± 0.15	0.07 ± 0.63	-0.04 ± 0.53	0.2 ± 0.92	0.0 ± 0.8
Change in creatinine UF	0.3		-0.3 ± 1.2	-0.9 ± 0.96	-0.01 ± 0.31	-0.6 ± 0.75	0.23 ± 0.7	-0.4 ± 0.71	0.2 ± 0.7
Death control	0 (0%)	11 (11%)	NA	0 (0%)	NA	NA	13 (13%	5 (25%)	4 (24%)
Death UF	1 (5%)	9 (9%)	NA	1 (4%)	NA	NA	16 (17%)	3 (15%)	4 (21%)
BNP control	NA	1309 ± 1494	370.6 ± 148.8	826 ± 913	NA	6707 ± 3597	4007		8946 ± 5981
BNP UF	NA	1256 ± 1203	706.3 ± 205.6	1066±1196	NA	5063 ± 3811	5013		8256 ± 8580

UF: donates Extracorporeal Venous Ultrafiltration; CAD: donates coronary artery disease; BNP: donates B-type natriuretic peptide.

heterogeneity (p = 0.46). Similarly, change in creatinine level was significantly higher in the intention-to-treat studies, but significantly lower in the per-protocol studies (Figure 5B). The data remained heterogeneous and non-statistically significant after stratification by randomized versus non-randomized studies and larger versus smaller sample size.

Sensitivity Analysis

Sensitivity analysis, revealed no evidence of changing magnitude in the pooled estimates for weight change over time. However, there may have been trends toward the null for change in creatinine levels and over-all mortality outcome during the study period. Exclusion of studies published after 2008 resulted in varying differences in the pooled estimates for the WMD associated with change in creatinine levels and weight loss; however the exclusion did not have a significant impact on the pooled estimates given the overlapping 95% confidence intervals with full-pooled effects when data from all studies were included for analyzing the outcomes—weight change and change in creatinine levels.

Discussion

The present analysis evaluated the clinical responses of UF treatment for reducing volume overload in ADHF patients and have compared the outcomes with that of standard diuretic approach. Our study demonstrated that a significant difference existed for change in mean body weight between the two treatment groups, but no significant difference was observed with regard to change in creatinine levels. Additionally, the mortality rates were similar in the two groups during the follow-up period. Hence this meta-analysis does not support prior observations that UF

Table 2 – Quality assessment of studies included in the Meta analysis

Author	Randomization	Allocation concealment	Blinding	Intention to treat analysis	Sample size calculation	Design
Bart 2005	Yes	No	No	Yes	Yes	RCT
Constanzo	Yes	No	No	No	No	RCT
Libetta	No	No	No	No	No	Non-randomized controlled trial
Bartone	No	No	No	No	No	Retrospective cohort
Rogers	Yes	No	No	No	No	RCT
Giglioli	Yes	No	No	No	Yes	RCT
Bart 2012	Yes	No	No	Yes	Yes	RCT
Badawy	Yes	No	No	No	No	RCT
Hanna	Yes	No	No	Yes	Yes	RCT

RCT: randomized control trials

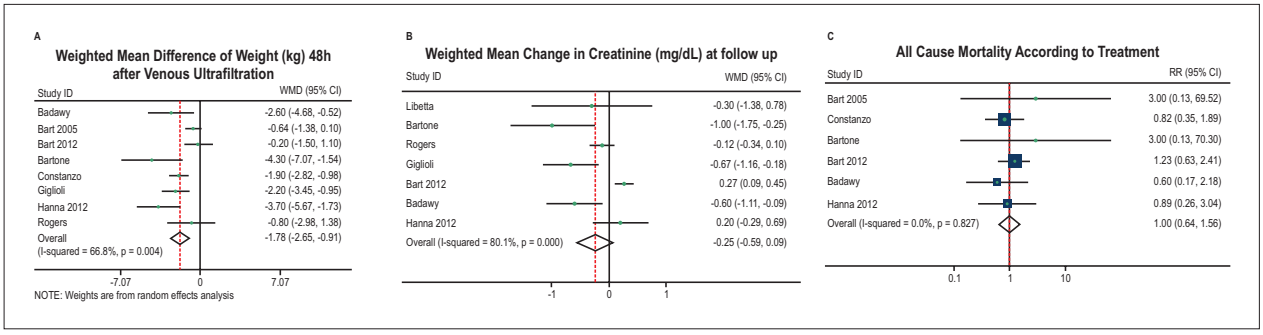

Figure 2 – *A: Forest plot comparing mean weight difference between the control and the intervention group. Squares represent weighted mean difference (kg) of patient's weight in the UF versus control group. B: Forest plot comparing mean difference in creatinine level between the control and the intervention group. Squares represent weighted mean difference (mg/dL) of creatinine level in the UF versus control group. C: Forest plot comparing relative risk of overall mortality. Squares represent relative risk of death in the UF versus control group. Size of square is proportional to study weight. Error bars represent 95% confidence interval. Diamonds represent pooled estimate for risk ratio with 95% CI.*

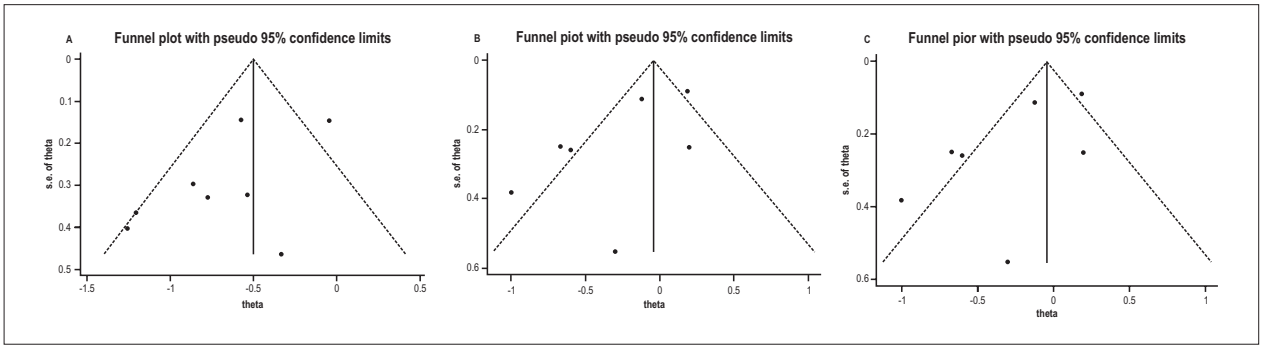

Figure 3 – *A: Funnel plot for visualization of publication bias across studies related to weight loss. B: Funnel plot for visualization of publication bias across studies related to change in creatinine level. C: Funnel plot for visualization of publication bias across studies related to mortality outcome.*

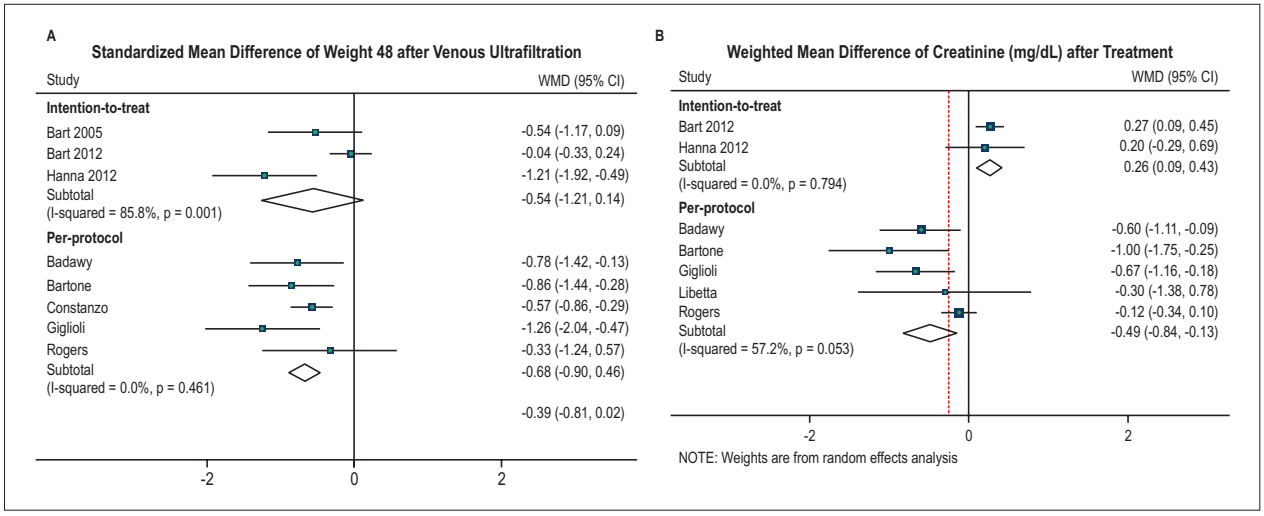

Figure 4 – *A: Results showing mean change in weight after 48 hours stratified by baseline BNP values. B: Results showing mean change in creatinine level stratified by baseline BNP values.*

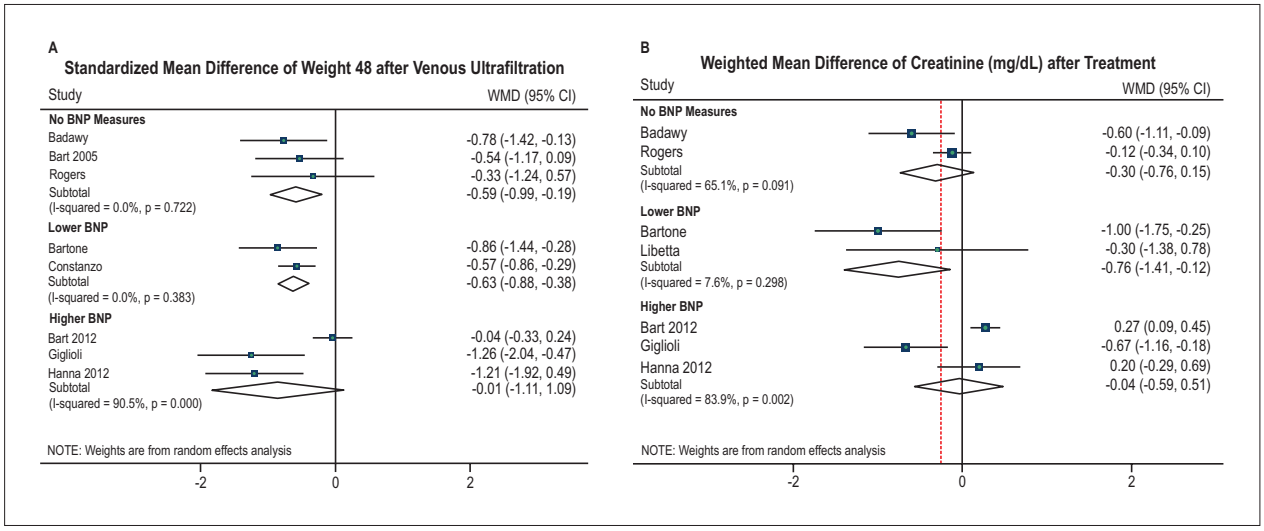

Figure 5 – *A Results showing mean change in weight after 48 hours stratified by intention-to-treat versus per-protocol analysis. B: Results showing mean change in creatinine level stratified by intention-to-treat versus per-protocol analysis.*

treatment option may improve volume overload, renal dysfunction or mortality rate in comparison with standard therapy using diuretics.

While some studies demonstrated that treatment with UF significantly reduced volume overload compared with traditional diuretic approach alone[9,23], findings from a more recent study contradicted these results[13]. The latter study included patients with severe renal dysfunction, and suggested that the need for early discontinuation of UF treatment due to clinical and technical reasons other than volume reduction was responsible for its failure to provide any beneficial effect with respect to weight change and lowering of creatinine levels. The same study also demonstrated that UF treatment was associated with an increased rate of adverse events such as subsequent kidney failure, bleeding, and catheter-related complications. Our analysis contradicted previous findings on weight loss. However, this was mainly observed in the studies dealing with lower BNP concentration and per protocol analysis. While the studies with intention-to-treat analysis demonstrated no significant changes in weight reduction, we detected a small significant increase in the creatinine levels. In clinical practice, the benefit of UF was restricted to those who were able to tolerate this therapy. Not only was the weight reduction benefit small, any benefit from this therapy appears to be restricted only to those individuals, who could tolerate this therapy such as individuals in the per protocol analysis as well as individuals with lower BNPs, who are also less likely to need advanced support.

The small change in weight detected in both groups can be explained in several ways. First, both therapies might not have been adequately fine-tuned to obtain maximum benefit. Second, patients might be too unstable or refractory to tolerate a more aggressive intervention. Lastly, patients might not be completely overloaded with fluid, as one would expect and as such not enough volume was lost in both groups. Although our meta-analysis is unable to fully answer this question, since the benefit was restricted to those studies that reported lower BNP values, it seems that the difference in weight loss was restricted to the less decompensated group of patients. Hence, we may suggest that severe cases of ADHF might not have tolerated more aggressive diuresis, regardless of the form of treatment applied.

Interestingly, our study showed that the benefit achieved with regard to weight loss and favorable creatinine changes were also limited to those studies with lower baseline BNP levels. Since BNP is a surrogate marker of ADHF severity, it was elevated in all studies. Moreover,, we did not witness any intervention benefits in those studies where the mean baseline BNP level was above the median value as calculated from the studies included in the meta-analysis. This finding suggested that the benefit of UF therapy might be restricted to those individuals with less severe ADHF and who could tolerate this therapy. However, this was also the group in which patients could be adequately managed by treatment with diuretics, and they did not require any advanced specialized care such as UF.

In addition, our study demonstrated that diuretics and UF therapeutic options had similar benefits with regard to overall mortality rate. This finding was not surprising since the most common causes of death in individuals with ADHF are sudden cardiac death due to arrhythmias, low-output states refractory to inotropic support, and infection; both interventions are intended for volume reductions and as such have no direct influence in reducing these outcomes.

Our study has several limitations. First, the heterogeneity in the results obtained for weight and change in creatinine level could only be partially explained by the stratified analysis although other study characteristics might explain our current findings. Second, our study did not account for variations stemmed from the designed dosage regimen of diuretics or the duration of UF and the variations might influence the overall disease prognosis. Finally, there are limitations in the studies selected such as allocation concealment or blinding or randomization, and only a few were analyzed in the intention-to treat analysis.

Although some of these subjects were addressed in the stratified analysis, residual confounding might still be present. Furthermore, just two of the nine total studies contributed 388 (63%) patients for analysis, although sensitivity analysis revealed that no single study had excessive influence on the results. Despite these limitations, our study has several strengths. First, our systematic literature search included all available scientific evidence and thereby reduces the likelihood of biased conclusions regarding clinical benefits of one treatment versus the other. Second, a homogeneous lack of all-cause mortality benefit was considered for both therapies. Finally, our work corroborated findings from existing literature by indicating that the benefits of UF might be limited to particular subgroups with favorable risk profiles.

Conclusion

Compared with standard therapy using diuretics, the use of UF in treating volume overload in ADHF was only moderately effective in reducing weight. However, we neither observed any significant reduction of serum creatinine level nor observed any improvement in the overall all-cause mortality rate. Though UF therapy might cause improvement in the fluid loss in selected populations, UF should not be universally recommended over standard therapy using diuretics in managing fluid status in ADHF patients particularly considering the lack of clear evidence supporting its beneficial effects coupled with the high cost associated with its use.

Author contributions

Conception and design of the research:Barkoudah E, Kodali S, Okoroh J, Sethi R, Suemoto C, Bittencourt MS. Acquisition of data: Barkoudah E, Kodali S, Okoroh J, Sethi R, Suemoto C, Bittencourt MS. Analysis and interpretation of the data: Barkoudah E, Kodali S, Okoroh J, Sethi R, Hulten E, Suemoto C, Bittencourt MS. Statistical analysis: Barkoudah E, Kodali S, Okoroh J, Sethi R, Suemoto C, Bittencourt MS. Writing of the manuscript: Barkoudah E, Kodali S, Okoroh J, Sethi R, Suemoto C, Bittencourt MS. Critical revision of the manuscript for intellectual content: Barkoudah E, Kodali S, Okoroh J, Sethi R, Hulten E, Suemoto C, Bittencourt MS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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