Liberal Versus Restricted Fluid Administration in Heart Failure Patients

A Systematic Review and Meta-Analysis of Randomized Trials

Yang LI,¹ RN, Biao FU,² MD, and Xiaoxian QIAN,³ MD

SUMMARY

Restrictive fluid intake is recommended, in addition to standard pharmacologic treatment, in the treatment of patients with chronic heart failure (CHF). However, this recommendation lacks firm scientific evidence. We conducted a systematic review and meta-analysis of published randomized controlled trials to estimate the effect of fluid restriction in patients with heart failure.

Randomized controlled trials were identified in the MEDLINE, EMBASE, and Cochrane databases using the search-keywords “fluid” and “heart failure”. Outcomes were compared in heart failure patients with liberal and restricted fluid intake. Pooled risk ratios (RR) and weighted mean differences (WMD) were calculated using random effects models. Studies focusing on decompensated heart failure were analyzed separately.

Six small randomized trials comparing liberal and restricted fluid intake met the inclusion criteria. Significant heterogeneity was noted in the reported studies for several outcomes. There were no differences in readmission rate (5 studies, pooled RR = 1.32; 95% CI: 0.86 to 2.01; $P = 0.2$), mortality rate (5 studies, pooled RR = 1.50; 95% CI: 0.87 to 2.57; $P = 0.14$), perceived thirst (4 studies, WMD = -0.7; 95% CI: -2.58 to 1.17; $P = 0.46$), duration of intravenous diuretics (2 studies, WMD = 0.17; 95% CI: -1.26 to 1.6; $P = 0.81$) or serum sodium levels (WMD = -1.61; 95% CI: -3.28 to 0.07; $P = 0.06$) between the liberal fluid intake group and the restrictive fluid intake group. Mean serum creatinine and BNP levels were significantly higher in the liberal fluid group: WMD 0.20 (95% CI: 0.15 to 0.25; $P < 0.00001$) and 172.59 (95% CI: 67.38 to 277.8; $P = 0.001$), respectively. There was no difference in any of the outcomes after correcting for heterogeneity.

While studies to date are limited by heterogeneity and small sample sizes, the combined data suggest similar clinical outcomes in patients with CHF managed with liberal and restrictive fluid intake. Larger studies are needed to confirm our findings. (Int Heart J 2015; 56: 192-195)

Key words: Fluid-restriction, Heart dysfunction, Water-intake

In addition to standard pharmacologic treatment, restrictive fluid intake is often used in the treatment of patients with heart failure.^{1,2} While international professional guidelines have recommended fluid restriction for patients with chronic heart failure (CHF), this recommendation lacks firm scientific evidence. This strategy can be stressful to patients and should be supported by better evidence of improved outcomes if it is to be widely used.

Prior studies comparing liberal to restricted fluid intake in heart failure patients are limited by small sample sizes, and their individual results do not permit firm conclusions to be drawn. In fact, recent studies have questioned the benefit of fluid restriction in heart failure patients.^{3,4} To synthesize and provide the best possible evidence for application in clinical practice, we conducted a systematic review and meta-analysis of published randomized controlled trials to estimate the effect

of fluid restriction in patients with heart failure.

METHODS

Literature search and study selection: Relevant trials were identified in the MEDLINE, EMBASE, and Cochrane databases by using the search-keywords “fluid” and “heart failure”. Published full-text randomized controlled trials (RCT) comparing liberal fluid to restricted fluid intake in heart failure patients were eligible. Studies of patients with both compensated and decompensated heart failure were included. We excluded nonrandomized studies, quasi-randomized designs, case reports, case series, and studies published in abstract form. We used the Cochrane collaboration tool for assessing risk of bias as quality assessment of the studies included in our analysis.

From the Divisions of ¹ Dermatology and ² Cardiology, Xinqiao Hospital, Third Military Medical University, Chongqing, and ³ Division of Cardiology, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China.

Address for correspondence: Biao Fu, MD, Division of Cardiology, Xinqiao Hospital, Xinqiao Road, Shaping District, Chongqing City, Chongqing 404000, China. E-mail: fbytt@qq.com

Received for publication September 6, 2014. Revised and accepted September 10, 2014.

Released in advance online on J-STAGE February 23, 2015.

All rights reserved by the International Heart Journal Association.

Outcomes measures: The primary study endpoints evaluated in this review were mortality, readmission, and discontinuation of intravenous (IV) diuretic therapy. Secondary outcomes were perceived thirst and levels of serum sodium, creatinine, and B-type natriuretic peptide (BNP). Sense of thirst was measured using a visual analog scale (VAS) ranging from 0 to 10, where 0 denoted “no thirst” and 10 “constant thirst”.

Data abstraction: Two investigators (F.B, L.Y) reviewed articles independently. RCTs that evaluated the effect of restrictive or liberal fluid intake in heart failure patients were included.

Discrepancies regarding the inclusion of studies and data abstraction were resolved by discussion. Data were entered into and analyzed using Review Manager 5.1.

Data synthesis: We assessed heterogeneity across trials using the Cochrane Q statistic and the I^2 statistic. Recognizing the modest statistical power of these tests for heterogeneity, we conservatively considered heterogeneity as significant for $P < 0.1$.

Pooling of data was considered if there were at least two studies available for a particular outcome. Pooled risk ratios (RR) and weighted mean differences (WMD) were calculated from abstracted data for categorical and continuous outcomes, respectively. We combined data using DerSimonian-Laird random-effects models even if no evidence of statistical heterogeneity was noted. This allows for variation in the true effect across studies and takes into account the limitations of the statistical tests for heterogeneity. This approach also provides more conservative estimates of effect size. When studies reported only medians, we approximated them as representing the mean. The width of the interquartile range was approximated as 1.35 standard deviations.⁵⁾ RRs for each categorical outcome from the different studies and WMDs for continuous data were plotted graphically as forest plots.

Sensitivity analyses were conducted to estimate the influence of each study on the pooled results by deleting each in

turn from the analysis and evaluating the change in the pooled treatment effect size. Finally, we assessed publication bias graphically using funnel plots and formally tested funnel asymmetry statistically.

RESULTS

Six randomized clinical trials, including one randomized cross-over study, were included in our analysis (Supplemental Figure 1). In all, 751 patients were randomized to either a fluid restriction group (range, 0.8-1.5 L/day) or free fluid intake group (Supplemental Table).^{3,4,6-9)} Two of the trials were conducted in patients with decompensated heart failure.^{3,4)} Patients with compensated heart failure were evaluated in the other 4 trials.^{6,9)} Sodium and fluid were both restricted in two studies,^{4,7)} and only fluid was restricted in 4 studies.^{3,6,8,9)} The length of follow-up was from 2 weeks to 8 months, with a median follow-up of 10 weeks.

Quality assessment of studies included: The Cochrane collaboration tool for assessing risk of bias showed some unclear risk in selection bias and high risk in attrition bias (16.7%) (Supplemental Figure 2).

Clinical outcomes: Five trials reported readmission rates. The frequency of readmission was 4.3% (161 of 376) in the liberal fluid group and 2.6% (98 of 373) in the restricted fluid group. The pooled RR of readmission in the liberal versus restricted fluid groups was 1.32 (95% CI: 0.86 to 2.01; $P = 0.2$) (Figure 1). There was no evidence of heterogeneity among these studies ($I^2 = 44\%$; $P = 0.13$).

Mortality was reported in 5 trials. The mortality rate was 8.5% (32 of 376) in the liberal fluid group and 5.6% (21 of 373) in the restricted fluid group. The pooled RR of mortality in the liberal versus restricted fluid groups was 1.50 (95% CI: 0.87 to 2.57; $P = 0.14$) (Figure 2), with no evidence of heterogeneity.

Figure 1. Forest plot of readmission rates with liberal versus restrictive fluid.

Figure 2. Forest plot of mortality rates with liberal versus restrictive fluid.

geneity among these studies ($I^2 = 0\%$; $P = 0.51$).

The assessment for publication bias for the primary outcomes (readmission and mortality) presented symmetric funnel plots (Supplemental Figure 3, 4).

Thirst was evaluated in 4 trials. The WMD of thirst in the liberal versus restricted fluid groups was -0.7 (95% CI: -2.58 to 1.17; $P = 0.46$) (Supplemental Figure 5). Significant heterogeneity was seen in these trials ($I^2 = 90\%$; $P < 0.0001$).

Two trials including patients with acute decompensated heart failure contained an evaluation of intravenous diuretic therapy. The pooled mean differences (MD) of duration of intravenous diuretics in the liberal versus restricted fluid groups was 0.17 (95% CI: -1.26 to 1.6; $P = 0.81$) (Supplemental Figure 6). There was no evidence of heterogeneity among these studies ($I^2 = 0\%$; $P = 0.74$).

Serum laboratory findings: Serum sodium levels were reported in 5 trials. There were no differences in mean serum sodium levels in the two groups. The pooled mean difference of sodium in the liberal versus restricted fluid groups was -1.61 (95% CI: -3.28 to 0.07; $P = 0.06$), with significant heterogeneity between trials ($I^2 = 100\%$; $P < 0.0001$).

Serum creatinine levels were also reported in 5 trials. The mean serum creatinine was significantly higher in patients managed with fluid restriction. The WMD in the liberal versus restricted fluid groups was 0.20 (95% CI: 0.15 to 0.25; $P < 0.00001$). There was significant heterogeneity between studies ($I^2 = 87\%$; $P < 0.00001$).

BNP levels were reported in 4 trials. The mean was significantly higher in the liberal fluid group. The WMD of BNP levels in the liberal versus restricted fluid groups was 172.59 (95% CI: 67.38 to 277.8; $P = 0.001$). There was evidence of significant heterogeneity between studies ($I^2 = 56\%$; $P = 0.03$).

Sensitivity analysis: Patient's evaluated by Paterna had the worst (LVEF < 35%) cardiac function of all the patients evaluated. Most of the heterogeneity found was related to this study. When this study was removed, no difference was found between liberal and restricted fluid intake in any of the outcomes: readmission (RR = 1.02; 95% CI: 0.65 to 1.58; $P = 0.94$; $I^2 = 0\%$), mortality (RR = 1; 95% CI: 0.31 to 3.26; $P = 1$; $I^2 = 0\%$), sodium levels (MD = 0.18; 95% CI: -0.46 to 0.81; $P = 0.59$; $I^2 = 0\%$), creatinine levels (MD = -0.03; 95% CI: -0.15 to 0.09; $P = 0.66$; $I^2 = 45\%$) and BNP levels (MD = -100.49; 95% CI: -301.17 to 100.19; $P = 0.33$; $I^2 = 0\%$).

Subgroup analyses:

Compensated heart failure Heterogeneity was also found among the trials that included only patients with compensated heart failure. In this subgroup, differences were found between liberal and restricted fluid intake on the rate of readmission (RR = 1.74; 95% CI: 1.43 to 2.11; $P < 0.00001$; $I^2 = 0\%$), mortality (RR = 1.50; 95% CI: 0.87 to 2.57; $P = 0.14$; $I^2 = 0\%$), thirst (MD = -0.36; 95% CI: -2.89 to 2.16; $P = 0.78$; $I^2 = 91\%$), sodium levels (MD = -2.22; 95% CI: -4.13 to -0.32; $P = 0.02$; $I^2 = 100\%$), creatinine levels (MD = 0.25; 95% CI: 0.21 to 0.28; $P < 0.00001$; $I^2 = 77\%$) and BNP levels (MD = 255.42; 95% CI: 196.22 to 314.63; $P < 0.00001$; $I^2 = 0\%$). Again, after excluding Paterna's study, no difference in any endpoint was found, including readmission rate (RR = 1.19; 95% CI: 0.7 to 2; $P = 0.52$; $I^2 = 0\%$), mortality (RR = 1; 95% CI: 0.31 to 3.26; $P = 1$; $I^2 = 0\%$), sodium level (MD = 0; 95% CI: -0.79 to 0.79; $P = 1$; $I^2 = 0\%$) and creatinine level (MD = 0.06; 95% CI: -0.06 to 0.18; $P = 0.29$; $I^2 = 0\%$).

No difference in serum laboratory outcomes was found between the liberal and restricted fluid groups in trials that studied patients with decompensated heart failure; sodium levels (MD = 0.49; 95% CI: -0.67 to 1.65; $P = 0.41$; $I^2 = 13\%$), creatinine levels (MD = -0.12; 95% CI: -0.26 to 0.01; $P = 0.08$; $I^2 = 7\%$) and BNP levels (MD = -100.86; 95% CI: -301.84 to 100.12; $P = 0.33$; $I^2 = 0\%$).

Sodium restriction In studies that used both fluid and sodium restriction, there were no differences between the liberal fluid and sodium group and restricted fluid and sodium group in readmission rate (RR = 0.78; 95% CI: 0.36 to 1.69; $P = 0.53$; $I^2 = 0\%$), thirst (MD = -0.39; 95% CI: -2.8 to 2.02; $P = 0.75$; $I^2 = 92\%$), sodium levels (MD = 0.44; 95% CI: -0.53 to 1.41; $P = 0.38$; $I^2 = 10\%$), creatinine levels (MD = 0.03; 95% CI: -0.09 to 0.15; $P = 0.63$; $I^2 = 12\%$) or BNP levels (MD = -182.52; 95% CI: -492.2 to 127.15; $P = 0.25$; $I^2 = 0\%$).

There was significant heterogeneity in the studies that used fluid restriction as the only intervention. Differences were found between liberal and restricted fluid intake on the rate of readmission (RR = 1.61; 95% CI: 1.16 to 2.22; $P = 0.004$; $I^2 = 24\%$), mortality (RR = 1.47; 95% CI: 0.75 to 2.89; $P = 0.26$; $I^2 = 11\%$), feelings of thirst (MD = -0.98; 95% CI: -4.7 to 2.74; $P = 0.61$; $I^2 = 90\%$), sodium levels (MD = -2.27; 95% CI: -4.19 to -0.36; $P = 0.02$; $I^2 = 100\%$), creatinine levels (MD = 0.23; 95% CI: 0.18 to 0.28; $P < 0.00001$; $I^2 = 87\%$), and BNP levels (MD = 219.12; 95% CI: 135.55 to 302.69; $P < 0.00001$; $I^2 = 40\%$). After excluding Paterna's study, no differences were found in readmission rate (RR = 1.15; 95% CI: 0.67 to 1.97; $P = 0.6$; $I^2 = 0\%$), mortality (RR = 1.1; 95% CI: 0.19 to 6.45; $P = 0.92$; $I^2 = 43\%$), sodium levels (MD = -0.05; 95% CI: -0.93 to 0.82; $P = 0.9$; $I^2 = 0\%$), or creatinine levels (MD = -0.09; 95% CI: -0.3 to 0.13; $P = 0.43$; $I^2 = 58\%$).

Other endpoints: Other assessments were performed in the randomized trials we evaluated. There were no differences in time to clinical stability, daily fluid output, or intravenous diuretic dose in the studies of patients with decompensated heart failure that used fluid restriction as the only intervention.³ No differences in the length of hospital stay or overall improvement were reported.⁴

The quality of life (QoL) of patients with stabilized heart failure improved during follow-up in the restricted fluid group in one study,⁶ and was similar between the groups in two other trials.^{7,8} There was no difference between the two groups in post-discharge heart failure, although the sample size was too small to adequately assess this outcome.⁶ Similar oral diuretic doses were reported in both groups.⁸ Patients described difficulty adhering to their fluid restrictions in two studies.^{6,8} Similar weight loss was reported in both groups in all studies reporting this outcome.^{3,4,7,8}

DISCUSSION

Fluid overload in patients with heart dysfunction can increase the heart's work, and lead to heart failure. Therefore, restriction of fluid is used as a key non-pharmacologic therapy for patients with heart failure. However, insufficient fluid volume as a result of fluid restriction can cause hypoperfusion of vital organs. Renal dysfunction and cardiac ischemia caused by hypoperfusion can contribute to heart failure. American and European guidelines for the non-pharmacological treatment of

chronic heart failure recommend fluid restriction in moderately to severely symptomatic patients.^{1,2} In the 2012 guidelines from the European Society of Cardiology (ESC), the recommendation was changed to 'avoid excessive fluid intake' and 'weight based fluid restriction'.¹⁰

Results of this meta-analysis suggest no benefit in mortality or readmission rates in patients with heart failure treated with fluid restriction. There was no benefit even in patients with decompensated heart failure. While serum creatinine and BNP might be impacted, there was heterogeneity among the trials, and sensitivity analysis suggested the finding was not robust. Patients evaluated by Paterna had the worst (LVEF < 35%) cardiac function of all the patients evaluated.⁹ After removing this study from the meta-analysis, there was no further evidence of heterogeneity and there were no group differences in any of the endpoints examined.

However, patients included in Paterna's study had the severest left ventricular dysfunction. In their study, they evaluated the effects of different diuretic doses (furosemide 250 mg/day versus 500 mg/day) and different levels of fluid intake (1000 mL/day versus 2000 mL/day), and obtained the same mortality results. However, this also suggested that high diuretic doses and fluid intake restriction leads to reductions in readmissions and BNP. Thus, it is impossible to come to the conclusion that fluid restriction has no benefit in heart failure. In the very least, fluid restriction may have an effect in patients with severe impairment of LVEF.

The finding that fluid restriction as the only intervention was not better than fluid and sodium restriction in patients with heart failure suggests that more evidence substantiating the benefit of sodium restriction is needed to support its use in the management of patients with heart failure.

To our knowledge, this is the first meta-analysis that compared liberal to restricted fluid in the management of CHF. We used a structured protocol for the literature search, study selection, and data synthesis. We assessed heterogeneity and explored sources using sensitivity analysis. We combined data using the more conservative random effects model even when no evidence of statistical heterogeneity was noted. This took into account clinical heterogeneity, which was likely present even in the absence of demonstrable statistical heterogeneity.

As in all meta-analyses, our findings are driven by the studies included and reflect the limitations of the primary studies. There was significant heterogeneity among studies. Some studies reported medians and interquartile ranges for continuous outcomes. We used appropriate statistical methods to estimate means and standard deviations to permit statistical pooling. Although this is a reasonable approach, we acknowledge the possibility of under- and overestimation. Finally, a major limitation of this report is the small number of patients included in the trials.

Conclusion: While fluid restriction is recommended by current guidelines for the treatment of patients with heart failure, results of this systematic review and meta-analysis suggest this therapy has no benefit in patients with heart failure. However, the studies to date are limited by heterogeneity and small sample sizes. Larger studies with sufficient power to evaluate important outcomes are needed to define the role of fluid restriction in the management of CHF.

DISCLOSURE

All authors declare that there is no conflict of interest requiring disclosure.

REFERENCES

1. Dickstein K, Cohen-Solal A, Filippatos G, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29: 2388-442. (Review)
2. Hunt SA, Abraham WT, Chin MH, *et al.* 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; 53: e1-90.
3. Travers B, O'Loughlin C, Murphy NF, *et al.* Fluid restriction in the management of decompensated heart failure: no impact on time to clinical stability. *J Card Fail* 2007; 13: 128-32.
4. Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da-Silva L. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. *JAMA Intern Med* 2013; 173: 1058-64.
5. Whitlock RP, Chan S, Devereaux PJ, *et al.* Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. *Eur Heart J* 2008; 29: 2592-600. (Review)
6. Albert NM, Nutter B, Forney J, Slifcak E, Tang WH. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *J Card Fail* 2013; 19: 1-9.
7. Philipson H, Ekman I, Forslund HB, Swedberg K, Schaefelberger M. Salt and fluid restriction is effective in patients with chronic heart failure. *Eur J Heart Fail* 2013; 15: 1304-10.
8. Holst M, Strömberg A, Lindholm M, Willenheimer R. Liberal versus restricted fluid prescription in stabilised patients with chronic heart failure: result of a randomised cross-over study of the effects on health-related quality of life, physical capacity, thirst and morbidity. *Scand Cardiovasc J* 2008; 42: 316-22.
9. Paterna S, Parrinello G, Cannizzaro S, *et al.* Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. *Am J Cardiol* 2009; 103: 93-102.
10. McMurray JJ, Adamopoulos S, Anker SD, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14: 803-69.

SUPPLEMENTAL FILES

Supplemental Table
Supplemental Figure 1, 2, 3, 4, 5, 6
Please find supplemental files;
http://www.jstage.jst.go.jp/article/ihj/56/2/56_14-288/_article/supplement