Comparison of continuous loop diuretic versus bolus injection regimens in patients with heart failure: a comprehensive meta-analysis of the literature

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INTRODUCTION

Heart failure (HF) is a challenging clinical syndrome and the leading cause of morbidity and mortality worldwide¹. In decompensated HF patients, diuretic administration is a crucial and first-line therapeutic option for reducing fluid overload by diuresis¹. Optimizing the loop diuretic dose is essential to produce a high proportion of loop diuretic transport in the proximal renal tubule, enabling it to optimally function on a Na⁺-K⁺-2Cl cotransporter on the luminal surface of the thick ascending limb of the loop of Henle². Theoretically, continuous infusion of a loop diuretic may be preferable to intermittent bolus injection treatment in terms of length of hospital stay, weight loss, and urine output³. Possible underlying reasons may include that continuous infusion of a loop diuretic may ensure better urine output and less neurohormonal stimulation due to the constant delivery rate of the loop diuretics to the tubule, resulting in less alteration in intravascular volume and fewer occurrences of adverse side effects³. Despite the fact that most randomized controlled trials (RCTs) supported a continuous infusion in regard to diuretic efficiency, there is no convincing evidence in the present literature to indicate that continuous infusion of a loop diuretic is preferable to bolus injection treatment or vice versa^{1,4}. As a result, we intended to perform a meta-analysis of RCTs that evaluated these two treatment options in HF patients.

METHODS

Data collection

We followed the recommended reporting items for systematic reviews and meta-analyses guidelines to report our results. Since the investigation was a meta-analysis, neither ethics committee approval nor patient informed consent was needed. First, we reviewed PubMed, Scopus, Google Scholar, and Cochrane libraries for relevant studies utilizing keywords such as "randomized controlled," "heart failure," "diuretic," and "continuous," "bolus," and "comparison." When all abstracts were reviewed, 39 studies remained out of 395 prospective investigations. Following an examination of the entire texts of the remaining articles, 21 studies were removed because they were duplicated and irrelevant, included meta-analyses, or had inaccurate results. Finally, the remaining 18 papers were subjected to our meta-analysis (Table 1).

Study evaluation

Two authors thoroughly reviewed the studies' applicability and bias probability. The studies were selected based on the following criteria: (1) prospective, randomized studies comparing intravenous (IV) continuous infusion of a loop diuretic to IV bolus injection of diuretics treatment in decompensated HF patients; (2) studies with at least in-hospital follow-up duration; (3) studies with the clinical outcomes, such as urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, estimated glomerular filtration (eGFR) change, and mortality; and (4) only furosemide treatment was used as the main diuretic regimen. Due to the possibility of selection bias, studies with a retrospective or observational design were not included in this meta-analysis. Finally, our meta-analysis excluded papers in which the effect size and standard error could not be calculated. All studies were evaluated using a modified Jadad scale with respect to study quality⁵. To assess the risk of bias, we used the Rob2 risk of bias tool as advised in the Cochrane Handbook for Systematic Reviews of Interventions (Supplementary 1)⁶.

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| Modified Jadad Scale | 5 | , urine length 6 / | , urine length 6 / | e, urine length 8 tality | , urine length 6 tality | , urine 6.5 | , urine 5.5 | , urine length 8 / | ium 3 | ium 4 | th of 4 | ge in 4 lity 4 | t, urine length 7 tality | ium 4 | , urine length 6 tality | ality 5 | :h of 5 | it loss, 7.5 stay, 7.5 | it loss 7 |
|---------------------------------------|---|--|--|--|--|--|---|--|---|--|--|--|--|-------------------------------------|--|---------------------------------------|--|--|---|
| End-points | Urine output | Change in creatinine output, weight loss, of hospital star | Change in creatinine output, weight loss, of hospital star | Change in creatinine output, weight loss, of hospital stay, mo | Change in creatinine output, weight loss, of hospital stay, mo | Change in creatinine output | Change in creatinine output | Change in creatinine output, weight loss, of hospital star | Urine output, sod excretion | Urine output, sod excretion | Urine output, leng hospital stay | Weight loss, chan creatinine, morta | Change in creatinine output, weight loss, of hospital stay, mo | Urine output, sod excretion | Change in creatinine output, weight loss, of hospital stay, mo | Weight loss, mort | Weight loss, lengt hospital stay | Urine output, weigh length of hospital mortality | Urine output, weigh |
| Continuous group sample size | 10 | 20 | 26 | 152 | 30 | 36 | 90 | 15 | 4 | 20 | 28 | 20 | 42 | 6 | 25 | 20 | 35 | 23 | 40 |
| Bolus group sample size | 10 | 21 | 30 | 156 | 28 | 37 | 30 | 14 | 4 | 20 | 28 | 20 | 39 | 6 | 25 | 20 | 35 | 19 | 40 |
| Total sample size | 20 | 41 | 56 | 308 | 58 | 73 | 60 | 29 | ω | 40 | 56 | 40 | 81 | 18 | 50 | 40 | 70 | 42 | 80 |
| Study design | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT | RCT |
| Duration of interventions (day) | 24 h | 48 h | 100 h | 72 h | 112 h | 24 h | 48 h | 48 h | 24 h | 24 h | 48 h | NA | 72 h | 48 h | 24 h | 24 h | 52 h | 72 h | 72 h |
| Dose of diuretics | Bolus: 324 (110.8) mg tid, continuous: 329 (186.7) mg/24 h | Bolus: 162 (48) mg bid, continuous: 162 (52) mg/24 h | Bolus: 172 (97) mg. continuous: 197 (148) mg/24 h | Bolus: 162 (52) mg bid, continuous: 162 (48) mg/24 h | Bolus: 160 (80) mg. continuous: 170 (70) | Bolus: 80 mg qid, continuous: 240 mg/10 h | Bolus: 100 mg bid, continuous: 100 mg/24 h | Bolus: 160 mg bid. continuous: 160 mg/24 h | Bolus: 145 (80) mg bid, continuous: 145 (80) mg/24 h | Bolus: 690 mg (250–2,000) bid, continuous: 690 (250–2000)/8 h | Bolus: 120 mg tid, continuous: 2-3 mg/h | Bolus: 20–100 mg, Continuous: 100–500 mg/4–10 h | Bolus: 200 mg. Continuous: 160 mg | Bolus: 90–120 mg tid, 60–80 mg/24 h | Bolus: 100 mg tid, continuous: 100 mg | Bolus: 120 mg tid, continuous: 5 mg/h | Bolus: 188 (64) mg, continuous: 197 (59) mg | Bolus: 80 mg bid, continuous: 80 mg/24 h | Bolus: 120/240 mg bid, continuous: 120/240 mg 24 h |
| Patient population | NA | LVEF: 35 (19%), NYHA II-IV | LVEF: 26.3 (13.6%), NYHA III-IV | LVEF: 35 (18%) | LVEF: 35 (9%) | LVEF: <35 in 50% patients, NYHA I-IV | LVEF: 33% (SD not available) | LVEF: 42.9 (13.1) | LVEF: 24 (5) | LVEF: NA | LVEF: <40%, NYHA II-IV | LVEF: NA, NYHA III-IV | LVEF: 57.4 (11), NYHA III-IV | NYHA III-IV | LVEF: 33.3% | NYHA III-IV | NA | НЕрЕЕ | LVEF: < 30% |
| Age | ΥN | 59.5 (14.9) | 53.5 (23.2) | 66 (13.6) | 71.9 (7.5) | 82 (9) | 59.3 (7.5) | 68.4 (11.7) | 54 (3) | 71 (11) | 66 (11.5) | 82.4 (3.1) | 66.4 (8.2) | 74.1 (SD not available) | 55.9 (SD not available) | NA | ЧЧ | 65.3 (11.6) | 60.9 (11.9) |
| Country | Israel | NSA | USA | NSA | Italy | Spain | India | Turkey | Norway | Netherlands | India | Sweden | China | Israel | India | Egypt | China | NSA | Italy |
| Year | 1997 | 2010 | 2010 | 2011 | 2015 | 2014 | 2014 | 2015 | 1997 | 1996 | 2020 | 2020 | 2021 | 1992 | 2017 | 2018 | 2016 | 2018 | 2020 |
| Study | Makhoul et al ⁷ . | Allen et al. ⁸ | Thomson et al.° | Felker et al. ¹⁰ | Palazzuoli et al. ¹¹ | Llorens et al. ¹² | Shah et al. ¹³ | Yayla et al. ¹⁴ | Aaser et al. ¹⁵ | Dormans et al. ¹⁶ | Shree et al. ¹⁷ | Sager et al. ¹⁸ | Zheng et al. ³ | Lahav et al. ¹⁹ | Malkiwodeyar et al. ²⁰ | Ragab et al. ²¹ | Wang et al. ²² | Sharma et al. ²³ | Frea et al. ²⁴ |

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Clinical end points

The major end points evaluated in this meta-analysis were urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, eGFR change, and mortality.

Statistical analysis

This meta-analysis was carried out using the R software version 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). For analyses of pooled risk ratio and standardized mean difference (SMD) with 95% confidence intervals, a "meta" package containing "metabin" and "metacont" was utilized. The Higgins I² and Cochran's Q tests were used to analyze study heterogeneity. In the case of moderate to high heterogeneity (I^2 >25%), the random-effect model was used to predict a pooled effect size, while the fixed-effect model was utilized in the case of low heterogeneity ($I^2 < 25\%$). To determine publication bias, Egger's regression test was chosen. A funnel plot was also utilized to detect any potential publication bias among publications. To identify the likelihood of the underlying source of between-study heterogeneity, outlier and influential analyses were conducted. After the outlier or influential study was eliminated, the pooled effect size was recalculated. A p-value of 0.05 was used to determine statistical significance (two-tailed tests).

RESULTS

The meta-analysis examined 18 RCTs^{3,7-24} with a total of 1,178 individuals (Table 1). The continuous infusion group (CG) had higher urine output than the bolus injection group (BG) (SMD=0.78 [0.11; 1.44], p<0.01) (Figure 1). The Eggers regression test was statistically meaningful for the pooled effect size for urine output (p<0.05), and I² was calculated as 87%, implying publication bias. A funnel plot revealed that the studies by "Dormans et al." and "Zheng et al." might have publication bias. Furthermore, these studies were also identified as outliers and influential articles. As a result, we eliminated these papers and repeated the pooled effect size for urine output. The overall heterogeneity dropped to 0%, and the CG still had higher urine output than the BG (SMD=0.40 [0.20; 0.61], p<0.01). In the subgroup analysis of urine output, the difference was significant between groups for 24-h urine output (p<0.01), whereas it was not significant between compared groups for 72 h (p=0.21). The CG actually had higher weight loss than the BG (SMD=0.39 [0.13; 0.65], p<0.01) (Figure 1). For weight loss, the study by "Zheng et al." was detected as might to be an outlier study and to have publication bias. So, the random-effect model was recalculated after

removing this study, and the CG had still higher weight loss than the BG (SMD=0.24 [0.14; 0.34], p<0.01). The CG excreted more sodium than the BG (SMD=0.61 [-0.73; 1.94], p<0.01) (Figure 1). However, there was high heterogeneity between studies regarding the results for sodium excretion. As the study by "Zheng et al." was suspected to have high bias according to the Rob2 bias assessment, we removed this study from the pooled effect for urinary sodium excretion, which indicated a nonsignificant difference between groups (p=0.29). Finally, there were no significant differences in terms of in-hospital duration, variations in serum creatinine, eGFR rates, and mortality rates between groups (Figure 2).

DISCUSSION

This meta-analysis showed that HF patients who received a continuous diuretic regimen had higher urine output and weight loss compared to a bolus regimen. There was no change between groups in terms of hospital stay, change in serum creatinine, eGFR, and mortality. The issue of sodium excretion should be examined in future meta-analyses with more recent studies.

The main therapy goal for congestive HF is fluid removal, resulting in decreased congestion and reduced afterload. This objective would enhance hemodynamics and improve HF symptoms, as well as prevent rehospitalizations and mortality²⁵. Loop diuretics, especially furosemide, are mainly used for this purpose via inhibiting salt and chloride reabsorption by acting on the Na⁺-K⁺-2Cl cotransporter in the thick ascending limb of the Henle loop⁴. The use of loop diuretics was recommended with a class IC indication in the recent guideline¹. However, the decision of using continuous versus bolus diuretic therapy has been left to the physician's discretion. Bolus therapy has the advantage of convenience of preparation and administration compared to continuous therapy. Unfortunately, it might not be able to achieve sufficient concentration to block sodium reabsorption²⁶.

The comparison of continuous diuretic therapy with a bolus regimen has been evaluated in RCTs and meta-analyses. This meta-analysis was more comprehensive than previous ones by including 17 RCTs. Amer et al. reported similar findings with this report that the continuous group had higher urine output and weight loss with no difference in the duration of hospital stay²⁷. However, they had a higher heterogeneity due to the study populations of RCTs included in their meta-analysis. Chan et al. found significant differences between groups with respect to urine output and weight loss, which was in accordance with our study²⁸. Kuriyama et al. showed significant differences between the continuous and bolus regimens

| | Conti | nuous(ml | (day) | в | olue(ml | (day) | Urine output Standardised Mean | | | |
|---|---|--|--|--|--|--|--|--|---|--|
| Study | Total | Mean | SD | Tota | l Mea | n SD | Difference | SMD | 95%-CI | Weight |
| Time = 72-hours | | | | | | | 1 : | | | |
| Allen et al. 2010 | 20 | 4894.0 | 2205.0 | 21 | 5113 | 0 2258 | .0 | -0.10 | [-0.71: 0.52] | 9.2% |
| Sharma et al. 2018 | 47 | 10748.0 | 2083.0 | 43 | 10300 | 0.0 1599. | .0 | 0.24 | [-0.18: 0.65] | 9.8% |
| Frea et al. 2019 | 40 | 10020.0 | 3032.0 | 40 | 8612 | .0 2984. | 0 | 0.46 | [0.02; 0.91] | 9.7% |
| Random effects model | 107 | | | 104 | | | | 0.26 | [-0.36; 0.87] | 28.6% |
| Prediction interval | | | | | | | | | [-1.56; 2.07] | |
| Heterogeneity: $I^2 = 5\%$, $\tau^2 = Test$ for effect in subgroup: | $t_2 = 1.8$ | 01, p = 0.3 0(p = 0.21) | 35 1) | | | | | | | |
| Time = 24-hours | | | | | | | | | | |
| Lorens et al. 2014 | 36 | 3705.0 | 1340.0 | 37 | 3093 | 0 1208 | 0 | 0 47 | [001.094] | 9.6% |
| Makhoul et al. 1997 | 10 | 3673.0 | 1353.0 | 10 | 2833 | 0 1042 | 0 | 0.67 | $[-0.24 \cdot 1.57]$ | 8.2% |
| Palazzuoli et al. 2014 | 30 | 2505.0 | 796.0 | 28 | 2140 | 0 468.0 | 0 | 0.55 | [0.02: 1.07] | 9.5% |
| Thomson et al. 2010 | 26 | 3726.0 | 1121.0 | 30 | 2955 | .0 1267. | .0 | 0.63 | [0.09: 1.17] | 9.4% |
| Aaser et al. 1997 | 8 | 2228.0 | 649.0 | 8 | 2460 | .0 663.0 | 0 | -0.33 | [-1.32: 0.65] | 7.8% |
| Dormans et al. 1996 | 20 | 2860.0 | 240.0 | 20 | 2260 | .0 150.0 | 0 | 2.94 | [2.02: 3.86] | 8.1% |
| Shree et al. 2020 | 28 | 1998.0 | 479.0 | 28 | 1614 | .0 703.0 | 0 | 0.63 | [0.09; 1.17] | 9.4% |
| Zheng et al. 2021 | 42 | 5146.0 | 621.0 | 39 | 3756 | .0 457.0 | 0 | 2.51 | [1.92; 3.10] | 9.3% |
| Random effects model | 200 | | | 200 | | | | 1.00 | [0.09; 1.92] | 71.4% |
| Prediction interval | | | | | | | | | [-1.64: 3.65] | |
| Heterogeneity: $I^2 = 88\%$, τ^2 Test for effect in subgroup: | $= 1.02^{\circ}$ $t_2 = 2.6^{\circ}$ | 16, p < 0.0 0 (p = 0.02) | 1 1) | | | | | | | |
| Random effects model | 307 | | | 304 | | | | 0 78 | [0 11. 1 44] | 100.0% |
| Prediction interval | 507 | | | 504 | | | | 0.70 | [-1 37 2 92] | 100.078 |
| Heterogeneity: $l^2 = 87\% \tau^2$ | = 0.81 | 36 0 < 0.0 | 1 | | | | | | [-1.57, 2.52] | |
| Test for overall effect: $z = 7$ | 69 (p < | (0.01) | | | | | -3 -2 -1 0 1 2 3 | | | |
| Test for subgroup difference | $es \cdot \gamma^2 =$ | 3.31 df = | 1(p = 0) | 07) | | | Eavours bolus Eavours continu | IOUS | | |
| rest for subgroup difference | ου. _{λ1} | 0.01, di | (p = 0. | 01) | | | | 1003 | | |
| | | | | | | | | | | |
| | | | | | | | Weight loss | | | |
| | | | | | | | | | | |
| Study | Tot | al Mean | n SD | (g) I Total | Bolus (k Mean | (g) SD | Standardised Mean Difference SM | D | 95%-CI W | eight |
| Study | Tot | al Mean | SD | Total | Bolus (Mean | (g) SD | Standardised Mean Difference SM | а го | 95%-CI W | eight |
| Study Zheng et al. 2021 Allen et al. 2010 | Conti Tot 4: | al Mean | 1.0 | (g) F Total 39 21 | 3.5 3.5 | (g) SD 0.7 2.3 | Standardised Mean Difference SM | D 9 3 [0 2 [-0 | 95%-CI W | eight 0.5% |
| Study Zheng et al. 2021 Allen et al. 2010 Felker et al. 2011 | 4: 20 15 | al Mean 2 4.7 0 2.7 2 3.7 | 1.0 2.4 4.7 | (g) 1 Total 39 21 156 | 3.5 3.5 1.6 3.1 | (g) SD 0.7 2.3 3.5 | Standardised Mean Difference SM | D 9 3 [0 2 [-0 4 [-0 | 95%-CI W 0.85; 1.81] 1 0.20; 1.04] { 0.08: 0.371 1 | eight 0.5% 3.2% 6.2% |
| Study Zheng et al. 2021 Allen et al. 2010 Felker et al. 2011 Thomson et al. 2010 | 42 15 | 2 4.7 2 2.7 2 3.7 6 6.8 | 1.0 2.4 4.7 6.1 | (g) F Total 39 21 156 30 | 3.5 3.5 1.6 3.1 5.1 | (g) SD 0.7 2.3 3.5 4.6 | Standardised Mean Difference SM | D 9 3 [0 2 [-0 4 [-0 1 [-0 | 95%-CI W 0.85; 1.81] 1 0.20; 1.04] 8 0.08; 0.37] 1 0.22; 0.84] 9 | eight 0.5% 3.2% 6.2% 9.7% |
| Study Zheng et al. 2021 Allen et al. 2010 Felker et al. 2011 Thomson et al. 2014 Palazzuoli et al. 2014 | 42 701 20 15 20 30 | August Inf Image: Second se | 1.0 2.4 4.7 6.1 2.1 | (g) F Total 39 21 156 30 28 | 3.5 3.5 1.6 3.1 5.1 3.8 | (g) SD 0.7 2.3 3.5 4.6 3.1 | Standardised Mean Difference SM | D 3 [0 2 [-0 4 [-0 1 [-0 3 [-0 | 95%-Cl W 0.85; 1.81] 1 0.20; 1.04] 8 0.08; 0.37] 1 0.22; 0.84] 9 0.29; 0.74] 9 | eight 0.5% 3.2% 6.2% 9.7% 9.9% |
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Figure 1. Forest plots of urine output, weight loss, and urine sodium excretion.

for urine output and weight loss but not for mortality, with similar findings reported in the current meta-analysis²⁹. In a recent review, Shastri et al. did not find a difference between treatment regimens regarding mortality, length of hospital stay, and weight loss³⁰. Compared to our study, fewer studies and sample size seem to have led to these results. Finally, Wu et al. conducted a meta-analysis and could not find a difference between continuous and bolus therapy groups⁴. The fact that some of the studies in the meta-analysis used torasemide instead of furosemide in the treatment and some of them were examined in all intensive care patients may also have contributed to these results. We included only studies that consisted of HF patients and used furosemide as a therapeutic agent in our meta-analysis.

There was high heterogeneity between studies in our meta-analysis. Most of them had an acceptable quality as



Figure 2. Forest plots of urine hospital stay, mortality, and serum creatinine change.

evaluated using the modified Jadad scale. Four studies were more likely to have a bias as assessed with Rob2^{3,7,12,17}. Blinding is an important factor for avoiding bias in RCTs. Only 7 of 18 RCTs were designed in blinded study design^{10-12,14,23,24}, in which 3 of them reported blinding methods^{14,23,24}. Another contributing factor that led to high heterogeneity in our meta-analysis might be the lack of a wash-out period in RCTs with a cross-over design^{9,15,16,19}. Additionally, most studies in this meta-analysis did not explain which statistical analyses were used to detect differences between groups in detail, for accounting loss follow-up, missing data, or analyses were conducted on an intention-to-treat versus per-protocol basis in the presence of nonadherence. It has been suggested that, on a per-protocol basis, the groups should be balanced with and adjusted for nonadherence³¹. Finally, furosemide was used in all RCTs as a diuretic agent, but the differences between the diuretic doses for both regimens of studies might have contributed to the existence of heterogeneity.

Limitations

This review had some limitations due to variances in basal characteristics of populations, various diuretic doses, and administration schedules, and using a concomitant medication, which were all the typical limitations of RCTs. Although the rate of mortality did not differ between compared groups, the mortality was calculated based on the risk ratio. So, it should be better to adjust for covariates and time. Unfortunately, none of the studies presented an adjusted hazard ratio for in-hospital mortality. Further meta-analyses with more RCTs might provide more information for the decision to use a continuous versus bolus diuretic regimen in HF patients.

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CONCLUSION

The continuous diuretic infusion had a higher diuretic effect and weight loss than the bolus diuretic regimen, without affecting serum creatinine, eGFR, and mortality in HF patients.

AUTHORS' CONTRIBUTIONS

FŞ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **TC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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