Continuous Versus Bolus Intermittent Loop Diuretic Infusion For Acutely Decompensated Heart Failure; Meta-Analysis

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Introduction

- The safety and efficacy of continuous infusion vs bolus injection of intravenous loop diuretics to treat acute decompensated heart failure were debated.
- Our aim is to compare the administration routes of diuretics in hospitalized patients with acute decompensated heart failure.

Methods

We followed the PRISMA statement guidelines during the preparation of this review and meta-analysis

Methods

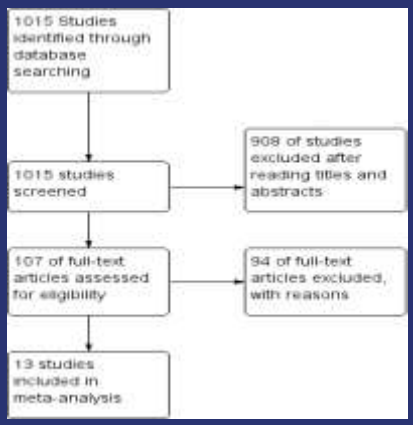
- ***Criteria for Considering Studies for this Review:***

1. Study design.
2. Intervention.
3. Comparator.
4. Population.
5. Outcomes.
6. Exclusion.

Methods

- ***Search Strategy:***
  - We searched MEDLINE/PubMed through March 2016 without any publication language limitation using The following MeSH search headings: heart or cardiac or congestive, failure, loop diuretics, furosemide, torsemide, bumetanide, and lasix.
  - These terms and their combinations were also searched as text-words. The "related articles" facility in PubMed was used to broaden the search,

Methods



Methods

- *Selection of Studies:*
  - Three authors applied the selection criteria.
  - Screening for eligibility was performed in two steps:
    1. The first step was to screen abstracts for eligibility using an online software product (Covidence ©).
    2. The second step, full-text articles of eligible abstracts were retrieved and screened for eligibility to the review.

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Methods

- *Data Extraction:*
  - Three authors (Qalawena M, El-Ameen N, and Akl H) extracted the data independently using a data extraction form.
  - The extracted data includes the following: 1) characters of study design, 2) characters of study population, 3) risk of bias domains, 4) study outcomes: urine output, body weight loss, complications including electrolyte imbalance, increase in creatinine, and tinnitus or hearing loss, duration of hospitalization, cardiac and all-cause mortality.
  - Data was exported from the form as MS excel sheet, and another two authors (Mousa M, and Meshref A) resolved disagreements.

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Methods

- ***Assessment of Risk of Bias in Included Studies:***
  - Two authors had independently assessed the quality of each included study in strict accordance with the Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011).
  - We used the quality assessment tables provided in (part 2, Chapter 8.5) the same handbook.
  - Disagreements between the reviewers were resolved by a third party.

Methods

- ***Measures of Treatment Effect:***
  - Urine output (in milliliters) was measured for 24, 48, or 72 hours.
  - Weight loss was calculated by accurate measurement of body weight (in kilograms) before and after treatment, from the patient's admission until day 3 or discharge from hospital.
  - Electrolyte imbalance was defined as the observation of hypokalemia or hypomagnesemia during treatment. Hypokalemia refers to a serum potassium level less than 3.5 meq/L, and hypomagnesemia means a serum magnesium level less than 1.5 mg/dL.

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Methods

- ***Measures of Treatment Effect (Cont.):***
  - Serum creatinine was measured from admission to day 3 or discharge, and changes were calculated accordingly.
  - Tinnitus or hearing loss was as reported by patients.
  - Cardiac mortality refers to cardiac arrest, sudden death, or death from cardiogenic shock.

Methods

- ***Dealing with Missing Data:***
  - When standard deviation (SD) of change in urinary output, body weight loss and duration of hospital admission was not provided, we calculated it from standard error or 95% confidence interval (CI) according to Altman *.

* Altman DGG, Bland JMM. Standard deviations and standard errors. BMJ 2005; 331(7521): 903.

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Methods

- ***Data Synthesis:***
  - Changes in urinary output, body weight loss and duration of hospital admission were pooled as SMD (standardized mean difference) in a meta-analysis model. We used RevMan version 5.3 for windows.

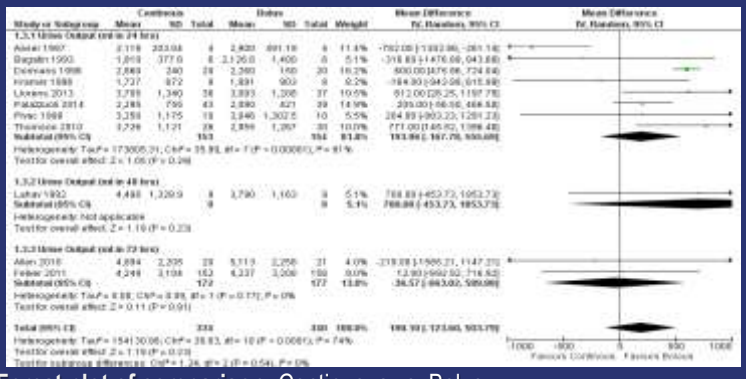
Methods

- ***Assessment of Heterogeneity:***
  - Heterogeneity was:
    - Assessed by visual inspection of the forest plots.
    - Measured by I-square and Chi-Square tests.
  - In case of a significant heterogeneity (Chi-Square P<0.1), sensitivity analysis was performed to resolve heterogeneity.

Methods

- ***Publication Bias:***
  - For assessment of publication bias, the pooled effect estimate was plotted against its SE in a funnel plot generated by RevMan software.
  - The existence of publication bias was determined by the degree of the figure's symmetry.

Results

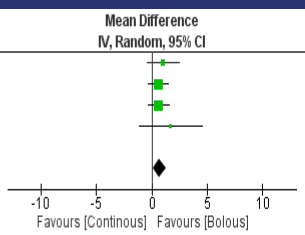


- **Forest plot of comparison:** Continuous vs. Bolus.
- **Outcome:** Urine output.

Results

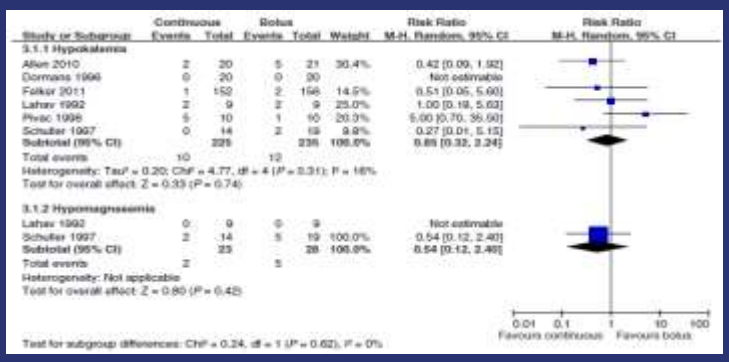
Study or Subgroup	Continous Mean	SD	Total	Bolus Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Allen 2010	2.66	2.44	20	1.64	2.34	21	16.2%	1.02 [-0.44, 2.48]
Felker 2011	3.67	4.67	152	3.08	3.54	156	40.5%	0.59 [-0.34, 1.52]
Palazzuoli 2014	4.1	1.9	43	3.5	2.4	39	39.1%	0.60 [-0.34, 1.54]
Thomson 2010	6.8	6.1	26	5.1	4.6	30	4.2%	1.70 [-1.16, 4.56]
Total (95% CI)			**241**			**246**	**100.0%**	**0.71 [0.12, 1.30]**

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)



- **Forest plot of comparison:** Continuous vs. Bolus.
- **Outcome:** Body weight loss.

Results



- **Forest plot of comparison:** Continuous vs. Bolus.
- **Outcome:** Incidence of electrolyte imbalance.

Results

- **Change in creatinine:** Three studies provided data on the increase in creatinine as a complication of diuretic therapy (Felker 2011, Allen 2010 and Schuller 1997).

- Our meta-analysis revealed no statistically significant difference between the continuous and bolus groups for the incidence of increased creatinine (CI,−0.09 to 0.09; P > .05). The heterogeneity is low in pooled effect (I^2 = 16%; χ^2 = 2.37; P = .31).

Results

- **Tinnitus or hearing loss:** Four studies had reported the complication of tinnitus or hearing loss (Kramer 1996, Lahav 1992, Pivac 1998 and Schuller 1997). There were 5 cases of tinnitus or hearing loss in 58 patients in the control group and 0 in 53 patients in the continuous group (RR, 0.09; 95% CI, 0.01-1.54).

- There was no significant difference in the incidence of tinnitus or hearing loss between continuous and control groups

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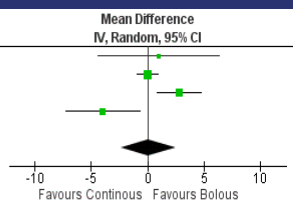
Results

Study or Subgroup	Continous Mean	SD	Total	Bolus Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Allen 2010	9.85	11.72	20	8.86	3.82	21	13.2%	0.99 [-4.40, 6.38]
Felker 2011	5	3.7	152	5	4.44	156	35.0%	0.00 [-0.91, 0.91]
Palazzuoli 2014	14.3	5	43	11.5	4	39	29.8%	2.80 [0.85, 4.75]
Thomson 2010	6.9	3.7	26	10.9	8.3	30	22.1%	-4.00 [-7.29, -0.71]
Total (95% CI)			**241**			**246**	**100.0%**	**0.08 [-2.36, 2.53]**

Heterogeneity: Tau² = 4.24; Chi² = 13.32, df = 3 (P = 0.004); I² = 77%
Test for overall effect: Z = 0.07 (P = 0.95)

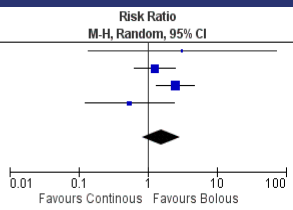


- **Forest plot of comparison:** Continuous vs. Bolus.
- **Outcome:** Duration of hospitalization.

Results

Study or Subgroup	Continous Events	Total	Bolus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allen 2010	1	20	0	21	3.8%	3.14 [0.14, 72.92]
Felker 2011	16	152	13	156	38.9%	1.26 [0.63, 2.54]
Palazzuoli 2014	25	43	9	39	42.8%	2.52 [1.35, 4.71]
Schuller 1997	2	14	5	19	14.5%	0.54 [0.12, 2.40]
Total (95% CI)		**229**		**235**	**100.0%**	**1.55 [0.83, 2.92]**
Total events	44		27			

Heterogeneity: Tau² = 0.14; Chi² = 4.64, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 1.37 (P = 0.17)



- **Forest plot of comparison:** Continuous vs. Bolus.
- **Outcome:** Cardiac mortality.

Advantages

- **The current review has provided relatively complete evidence than previously available, for a number of reasons:**

1. Body weight loss is a parameter that has been used only in the more recent studies and was included in our analysis.
2. We performed a subgroup analysis of urine output to clarify the cause of heterogeneity.

Limitations

1. Small patient numbers.
2. Crossover designs without an adequate washout period.
3. Differing diuretic schedules and dosages.
4. Use of concomitant drugs.
5. The wide range of publication dates in the included studies.

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Conclusions

- This meta-analysis showed that patients treated with either continuous or bolus loop diuretics demonstrated a similar urine output.

- Although the continuous group lost more weight than the bolus group, meta-analysis of the existing limited studies could not confirm any significant difference in the efficacy and safety with continuous administration of loop diuretic, compared with bolus injection in patients with acute decompensated heart failure.

Thank you

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