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Review Article

Continuous Infusion versus Intermittent Bolus Injection of Furosemide in Critically Ill Patients: A Systematic Review and Meta-analysis

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Objective: Fluid overload is a common phenomenon seen in intensive care units (ICUs). However, there is no general consensus on whether continuous or bolus furosemide is safer or more effective in these hemodynamically unstable ICU patients. The aim of this meta-analysis was to examine the clinical outcomes of continuous versus bolus furosemide in a critically ill population in ICUs.

Data Sources: MEDLINE, EMBASE, PubMed, and the Cochrane Database of Systematic reviews were searched from their inception until June 2017.

Review Methods: All randomized controlled trials, observational studies, and case-control studies were included. Case reports, case series, nonsystematic reviews, and studies that involved children were excluded.

Results: Nine studies (n = 464) were eligible in the data synthesis. Both continuous and bolus furosemide resulted in no difference in all-cause mortality (7 studies; n = 396; I^2 = 0%; fixed-effect model [FEM]: odds ratio [OR] 1.15 [95% confidence interval (CI) 0.67-1.96]; p = 0.64). Continuous furosemide was associated with significant greater total urine output (n = 132; I^2 = 70%; random-effect model: OR 811.19 [95% CI 99.84-1,522.53]; p = 0.03), but longer length of hospital stay (n = 290; I^2 = 40%; FEM: OR 2.84 [95% CI 1.74-3.94]; p < 0.01) in comparison to the bolus group. No statistical significance was found in the changes of creatinine and estimated glomerular filtration rate between both groups.

Conclusions: In this meta-analysis, continuous furosemide was associated with greater diuretic effect in total urine output as compared with bolus. Neither had any differences in mortality and changes of renal function tests. However, a large adequately powered randomized clinical trial is required to fill this knowledge gap.

Key Words: continuous; furosemide; intermittent; length of stay; loop diuretic; mortality; critically ill

FLUID OVERLOAD often is encountered in critically ill patients and has been demonstrated to be associated with adverse outcomes, namely cardiac failure, pulmonary edema, poor tissue healing, and impaired bowel function.[1–4] The outlook of recovery after these complications is poor and contributes to significant healthcare cost due to prolonged duration of ventilation and length of intensive care unit (ICU) stay.[3,5] A loop diuretic is the fundamental pharmacologic

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therapy to increase urine output to minimize the risk of multiorgan dysfunction in these hemodynamically unstable patients in ICUs.[6] To date, there is no general consensus on whether continuous infusion or intermittent bolus injection of furosemide is superior in terms of safety and efficacy profiles in these critically ill patients.

Furosemide is one of the most commonly used loop diuretics in ICUs. The half-life of furosemide varies between 1 and 1.5 hours.[7] Continuous infusion of furosemide is believed to confer additional benefits over bolus injection with less variability in the peak plasma furosemide concentration, leading to a constant predictable urine output and lower risk of electrolyte disturbance.[7,8] In addition, continuous infusion can be titrated easily to meet the expected diuresis effect as the fluid status of these critically ill patients fluctuates rapidly throughout the day due to multiorgan failure.[9]

In the literature, the findings of the only existing meta-analysis examining the optimal mode of furosemide administration in ICUs in 2011 were inconclusive, based on 4 small heterogeneous studies with a sample size of only 129 patients.[6] In recent years, several randomized controlled trials (RCTs) were published with conflicting results.[10–13] Intravascular volume fluctuation, drug toxicity, and tolerance from the different modes of furosemide administration remain unclear.[14,15] The clinical characteristics of the ICU population are unique and different from other hospitalized patients due to their vulnerable and already compromised hemodynamic status. Any fluid or electrolyte imbalance secondary to injudicious use of furosemide can be detrimental. The authors hypothesized that continuous furosemide was more physiologically friendly with better diuretic effects and lesser adverse effects than bolus injection in ICU patients.

The primary aim of this systematic review and meta-analysis was to examine the clinical outcomes of continuous infusion versus bolus injection of intravenous furosemide on mortality and length of hospital stay in critically ill patients with fluid overload. The secondary aim was to examine the diuretic effects and changes in estimated glomerular filtration rate (eGFR) and creatinine of continuous versus bolus furosemide in critically ill patients.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement 2015.[16] The review protocol was registered on the global public database of systematic reviews, PROSPERO (www.crd.york.ac.uk), with the reference number CRD42017067722. The research questions were formulated using a PICO approach (Supplemental Table 1).

Search Strategy

According to Mehta and Bouchard, fluid overload implies a degree of pulmonary edema or peripheral edema in critically ill patients.[1] It also is defined as $\geq 15\%$ in men and $\geq 13\%$ in women of fluid excess in relation to the extracellular volume.[17] Ovid, MEDLINE, EMBASE, PubMed, and the Cochrane Database of Systematic Reviews were searched from their inception until June 2017. The search strategy and terms used are provided in the online digital supplement (Supplemental Table 2). Publications not written in the English language were excluded. The bibliographies of included papers and relevant systematic reviews were hand-searched for additional papers. Experts and authors of papers identified in the search strategy were contacted for additional data or missing data.

Outcomes

Co-primary outcomes were all-cause mortality and length of hospital stay. Prespecified secondary outcomes were total urine output in the first 24 hours and changes in serum creatinine during the duration of treatment. Other relevant outcomes were considered for the meta-analysis if they were measured in more than one of the included studies. On this basis, changes in eGFR also were included. However, the incidence of acute kidney injury and need for renal replacement therapy were not reported in this review due to lack of sufficient data.

Study Selection and Data Extraction

Titles and abstracts were independently screened against eligibility criteria by 2 authors (A.L. and A.V.). The same 2 reviewers independently screened full texts of qualifying papers. Any disagreements at any stage were resolved by the third reviewer (K.N.). Inclusion criteria were (1) RCTs; (2) case-control studies; and (3) observational studies comparing the effects of continuous versus bolus injection of furosemide on the outcomes of mortality, length of hospital stay, total urine output, changes of creatinine, and eGFR in the critically ill population with fluid overload in the setting of ICUs.

Case reports, case series, and nonsystematic reviews were excluded. Studies involving patients younger than 16 years of age also were excluded. All the included RCTs and observational studies were assessed for risk of bias using the Cochrane Collaboration Risk of Bias Assessment Tool (https://handbook.cochrane.org) and the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca), respectively. In the Newcastle-Ottawa scale, studies with scores ≥ 7, 4 to 6, and < 3 were considered as having a low, moderate, and high risk of bias, respectively. In addition to the measured outcomes, the data fields, namely citation, year of publication, study design, country, population, sample size, and mean daily dose of furosemide, were extracted. Continuous outcomes presented as median (range) were converted to mean (standard deviation).[18]

Statistical Analysis

Statistical analyses were undertaken using RevMan Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Analyses of funnel plots were not undertaken for all co-primary and secondary outcomes because there fewer than 10 studies for each measured outcome to assess

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