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The impact of ultrafiltration in acute decompensated heart failure: A systematic review and meta-analysis ☆☆

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ABSTRACT

Background: A number of small studies suggest that ultrafiltration (UF) can improve outcomes in patients with acute decompensated heart failure (ADHF), but substantial uncertainty remains. We conducted a systematic review and meta-analysis with the primary goal of assessing the impact of UF on all-cause mortality in adults with ADHF; the secondary outcomes included re-hospitalization, emergency outpatient visits, and potentially deleterious effects (worsening renal function).
Methods: We searched the Medline (1966–2013), the Embase (1966–2013), the Cochrane Registry, the U.S. Clinical Trials databases (2000–2013) and the abstracts from key scientific meetings to identify studies comparing UF with usual care (diuretic therapy) in adults hospitalized with ADHF. We identified six randomized controlled trials enrolling 523 patients. Studies were not heterogeneous and a fixed effect model was used for all analysis.
Results: Unadjusted mortality was 13.3% among all diuretic patients as compared to 13.4% among UF recipients ($p = 0.81$). When compared to treatment with diuretics alone, UF did not reduce all-cause mortality (HR: 0.99, 95% CI: 0.60 to 1.61; $p = 0.65$), re-hospitalizations for HF (HR: 0.96, 95% CI: 0.39 to 2.35; $p = 0.92$), or unscheduled visits for heart failure (HR: 0.94, 95% CI: 0.36 to 2.50; $p = 0.84$). Furthermore, UF was not associated with increased risk of worsening renal function when compared to diuretic therapy (HR: 1.41, 95% CI: 0.89 to 2.22; $p = 0.89$).
Conclusions: UF does not appear to reduce mortality, re-hospitalization or unscheduled HF visits in adults with ADHF. At the present time data are insufficient to support routine use of UF for acute HF.

Introduction

Approximately one million Americans are hospitalized annually for heart failure (HF) at a cost of approximately $40 billion [1]. Despite advances in pharmacotherapy and medical devices, HF remains a progressive condition characterized by frequent exacerbations and hospital admissions. For patients with acute decompensated heart failure (ADHF), diuretics have been the mainstay of treatment for decades. However, even with optimal diuretic use, approximately 5% of patients with ADHF die during their acute hospitalization [1]. Ultrafiltration (UF) is a type of membrane filtration where hydrostatic pressure forces plasma water across a semipermeable membrane allowing movement of water and small solutes (less than 20 KDa) based on the trans membrane pressure gradient between the blood and the filtrate sides of the filter [2]. UF has been available since the 1970s but has recently received renewed attention because of promising results in a number of small studies [3,4]as well as increased interest in finding more effective therapies for ADHF. The uncertainty over UF is reflected in a number of clinical guidelines. Previous studies evaluating UF for treatment of ADHF have mostly focused on intermediate endpoints (e.g., degree of volume removal, weight loss) and have shown mixed results [3,5]. Moreover, a benefit of UF on hard clinical endpoints (e.g., mortality, re-hospitalization) has not been consistently demonstrated. Current American college of cardiology (ACC)/American Heart association (AHA) guidelines categorize UF as a class IIa recommendation recognizing that it is reasonable to apply this therapy in refractory congestion but that additional studies are needed to define situations where patients are most likely to benefit.

In an effort to better elucidate the risks and benefits associated with UF, we performed a systematic literature review and meta-analysis of the published and unpublished literature. Specifically, we set out to examine the effectiveness of UF as compared to "usual care" for patients hospitalized with ADHF. We evaluated the impact of UF on mortality, re-hospitalization and unscheduled HF visits. We also sought to examine its impact on renal function, a potential adverse effect encountered in clinical practice.

☆☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Methods

Our analysis is based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group [6].

Search strategy

With the assistance of a trained research librarian, we searched the Medline (1946–2013), the Embase (1966–2013), the CINAHL (1981–2013), the Web of Science (1899–2013), the Scopus (1960–2013), the Cochrane Database of systematic Reviews (2005–2013), the Cochrane Central Register of Controlled Trials (1898–2013), and the U.S. Clinical Trials databases (2000–2013) to identify randomized controlled trials and observational studies that compared UF to "usual care" (diuretic therapy) in patients with ADHF. In addition, we reviewed meeting abstracts for the 2000–2012 American College of Cardiology, the American Heart Association, the European Society of Cardiology, the Heart Failure Society of America and the European Society of Heart Failure. We also reviewed the reference lists of key articles to identify additional studies of potential relevance to our review. Search terms included the MeSH headings for "diuretics", or "epithelial sodium channel blocker", or "epithelial sodium ion channel blocker", or "sodium potassium chloride symporter", "heart decompensation", "myocardial failure", "mortality", "usual care", "standard of care", "renal failure", "re-hospitalization", "ultrafiltration", or "CVVH", "cohort as topic", or "observational study", "randomized controlled trials as topic", or "random allocation", or "clinical trial". A full description of our search strategy is included as Appendix1.

Study selection

We applied the following inclusion criteria in our review of potentially eligible studies: 1. prospective randomized controlled trials (RCTs) and/or observational studies; 2. adult patients aged > 18 years; 3. patients admitted with ADHF presenting with at least two signs of volume overload (lower extremity edema, pleural effusion or pulmonary edema on chest imaging, jugular venous pulsation > 10 cm water) and 4. report of one-or-more study outcomes for both the UF and control groups (all-cause mortality, re-hospitalization for any cause, unscheduled medical visits for HF (whether office or emergency department visits) and change in renal function at discharge). Control groups typically received usual care, though the precise definition of usual care differed across studies as described below.

We excluded studies if: 1. we were unable to obtain both the numerator (i.e., number of patients experiencing a given outcome) and denominator (i.e., number of patients at risk) for the UF and control groups; 2. data appeared to duplicate another study; and 3. diuretics were not withheld on admission in the UF group. In the UF group, diuretics were withheld during the filtration session and were resumed afterwards with optimal dosing left to the discretion of the physicians; thus, any potential benefit would solely be attributed to UF.

Methodological quality

We evaluated trials for concealment of treatment allocation, clear description of the design and completeness of follow up. The JADAD scale was used to score study quality (range of 0–5, higher scores indicating higher quality) [7].

Data abstraction

We used a structured abstraction instrument (Appendix 2) to collect study-level data including: 1. publication details (first author's last name, publication year); 2. study design (RCT or cohort); 3. patient characteristics (age, sex, race and co-morbidities including hypertension, diabetes, coronary artery disease); 4. type of device used (UF group only); 5. rate and duration of filtration (UF group only); and 6. dose and method of diuretic administration-bolus versus continuous (usual care group only).

Data extraction and information on study design, clinical and safety outcomes were performed independently by 2 reviewers (N.M. and S.M.). Discrepancies were resolved by consensus.

Outcome measure

The primary endpoint was all-cause mortality. The secondary endpoints included: 1. re-hospitalization for any cause; 2. unscheduled visits for HF (whether office or emergency department visits) and 3. worsening of renal function at hospital discharge. Worsening of renal function at discharge (varied from 24 to 96 h since admission) was defined as either an elevation in serum creatinine (greater than 0.3 mg/dl) or new requirement for dialysis [8].

Statistical analysis

We used graphical and tabular methods to summarize the results of our literature search and systematic review. We presented key information about eligible studies (e.g., authorship, study year, setting) using summary Tables. We calculated summary hazard ratios and 95% confidence intervals for all clinical outcomes (e.g., mortality, re-hospitalization) by pooling published raw data available for each study using standard meta-analytic methods. We attempted to obtain individual patient-level data from the authors of published studies to allow for more detailed pooling, but our efforts were unsuccessful. Hazard Ratios (HRs) were transformed logarithmically since they do not follow a normal distribution. The standard error was calculated from Log HR and the corresponding 95% confidence interval. We used the inverse variance method to achieve a weighted estimate of the combined overall effect [6].

We assessed the results for heterogeneity in our analysis by examining the forest plots and then calculating a Q statistic, which we compared with the I^2 index. The Q statistic indicates the statistical significance of the homogeneity hypothesis and the I^2 index measures the extent of the heterogeneity [9]. We considered the presence of significant heterogeneity at the 5% level of significance (for the Q test) and values of I^2 exceeding 56% as an indicator of significant heterogeneity according to established methods [10]. Combined estimate was obtained using the fixed-effects model (Mantel–Haenszel method) [6]. Publication bias was assessed by visual examination of the funnel plots and by using Egger's asymmetry test [11].

We conducted a number of sensitivity analyses to evaluate the robustness of our findings. In particular, we evaluated UF in: 1. studies that used newer less invasive techniques as shown in Table 1; 2. all studies except those utilizing high filtration rates of 500 ml/h [4,12] as they are less commonly utilized in clinical practice; 3. all studies except those using a single 8 hour filtration session [12] as it increases the risk of hypotension and 4. studies with more than 30 day follow up.

All probability values were 2 tailed and $p = .05$ was considered statistically significant. All analyses were performed using Microsoft excel version 2010. Our meta-analysis was considered to be exempt from institutional review board (IRB) review as per University of Iowa IRB guidelines since we did not obtain or had access to individually identifiable human participant information.

Results

Studies and patient characteristics

The literature search yielded 473 potential studies. After application of all inclusion/exclusion criteria we identified six RCTs and no cohort studies for inclusion in our final analysis (Fig. 1). Study quality was generally low-to-intermediate (four studies with JADAD scale of 2 and two with scale of 3) [4,13]. Table 1 shows characteristics of the included