Basic Science and Experimental Studies

Is Addition of Vasodilators to Loop Diuretics of Value in the Care of Hospitalized Acute Heart Failure Patients? Real-World Evidence From a Retrospective Analysis of a Large United States Hospital Database

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ABSTRACT

Background: Current guidelines recommend the use of intravenous (IV) vasodilators in addition to IV loop diuretics for the treatment of acute heart failure (AHF) patients without hypotension. The evidence basis for these recommendations is limited.

Methods and Results: Hospital billing records for 82,808 AHF patients in the United States were analyzed. Patients receiving IV loop diuretics alone were paired with patients receiving IV loop diuretics + IV nitrates or IV nesiritide with the use of propensity score matching, excluding those with hypotension and/or evidence of cardiogenic shock, myocardial infarction, or acute coronary syndrome. Compared with paired patients receiving IV loop diuretics alone, in-hospital mortality was similar among IV loop diuretics + IV nitrates patients (n = 4,401; 1.9% vs 2.0%; $P = .88$) and marginally higher for IV loop diuretics + IV nesiritide patients (n = 2,254; 2.2% vs 3.1%; $P = .05$). Compared with paired IV loop diuretics patients, IV loop diuretics + IV nitrates or IV nesiritide had longer lengths of stay (+1.6 and +2.1 days; $P < .01$) and 57% higher costs ($P < .01$).

Conclusions: Among hospitalized AHF patients, the addition of IV vasodilators to IV loop diuretics did not lower inpatient mortality or rehospitalization rates compared with loop diuretics alone, and was associated with longer lengths of stay and higher hospitalization costs. Although the lack of complete clinical, socioeconomic, and post-discharge data may have confounded these results, this analysis questions whether currently available IV vasodilators can improve outcomes in hospitalized AHF patients. (*J Cardiac Fail 2014;20:853−863*)

Key Words: Acute heart failure, claims data, hospital length of stay, hospitalization costs, nitrates.

Acute heart failure (AHF) has emerged as a clinically challenging entity, characterized by increasing incidence, high morbidity and mortality, and significant costs.[1−3] AHF is associated with >1 million annual hospitalizations in the United States (USA) alone, with European countries also reporting high AHF rates and associated costs.[2,4−6] Although a recent USA study has suggested that the rate of heart failure (HF)−related hospitalizations has stabilized over the past decade, the prevalence of chronic HF, and subsequent AHF hospitalizations, is projected to grow.[7] This growth is attributed to a corresponding increase in the aging population, an increase in the prevalence of HF comorbidities, and the improvement in patients' survival after

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myocardial infarction.[8] Because little advancement has been observed in AHF treatment options over the past decades, the short-term outcomes remain dismal,[9] with mortality rates or rehospitalization in the USA reaching 30%−50% within 60−90 days after 1st (index) AHF hospitalization.[10]

Current pharmacotherapy guidelines for inpatient AHF management are largely opinion-based, with none of the recommendations supported by level A evidence.[5] A clinical presentation of AHF with volume overload necessitates the initiation of intravenous (IV) loop diuretics as early as possible, supplemented by vasodilators such as IV nitroglycerin and nesiritide in the absence of systemic hypotension.[5,11] Vasodilators have been widely used for the treatment of AHF in the USA and Europe since the 1970s, based on studies demonstrating improvement in hemodynamic parameters following their administration.[12−14] There is, however, little evidence from controlled clinical trials that the addition of these drugs provides additional clinical benefit or improves outcomes compared with the use of IV loop diuretics alone.[15−17] Indeed, an analysis of AHF patient registry data[18] showed no significant difference in inpatient mortality for IV nitroglycerin (n = 6,549) versus IV nesiritide (n = 5,220). Similarly, the ASCEND (A Study of Cardiovascular Events in Diabetes) trial (n = 7,141) showed no effects on mortality or 30-day rehospitalization rates with IV nesiritide compared with placebo in addition to standard of care. Nesiritide was associated with only a small nonsignificant beneficial effect on dyspnea.[19]

Given the limited data in the literature regarding the incremental benefits of IV vasodilators as add-ons to diuretics, we undertook a large-scale population-based ''real-world'' study to assess inpatient treatment outcomes among USA patients hospitalized for AHF and treated with IV loop diuretics alone versus loop diuretics in combination with each of the most widely used vasodilators, specifically IV nitrates or IV nesiritide.

Methods

Data Source

Hospital billing records from the Thomson Reuters Marketscan Hospital Drug Database (HDD) were analyzed. These data are derived from ~600 teaching and nonteaching USA-based hospitals and capture all inpatient services provided by the hospitals for all admissions. Data include patient demographic characteristics, service level information for each hospital day, International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes for clinical diagnoses and procedures, drug utilization, department of service, discharge status, and financial costs and charges. Data from hospitalizations occurring from January 2007 to December 2009 were analyzed.

Study Population

A retrospective cohort study design, consisting of patients with ≥1 hospitalization with a primary diagnosis of AHF (ICD-9-CM 428.21, 428.23, 428.31, 428.33, 428.41, or 428.43) was used. Patients were excluded if they were <18 years old, had a diagnosis of hypotension (ICD-9-CM 458.xx) or cardiogenic shock (ICD-9-CM 785.51), had a nonemergency admission type (eg, elective surgery), or were transferred to another facility on the same day as the hospital admission. If the first AHF hospitalization of a patient met the entry criteria, the patient was included in the analysis and the hospitalization was marked as the index AHF hospitalization. Rehospitalizations were observed only if the patient was admitted to the same hospital; tracking admissions of the same patient across hospitals was not possible.

Treatment cohorts were defined based on the IV medications used during the index hospitalization for AHF. Treatments of interest included IV loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid), IV nitrates (nitroglycerin, glyceryl trinitrate, isosorbide dinitrate), and IV nesiritide. Mutually exclusive treatment cohorts compared in this analysis consisted of IV loop diuretics alone, IV loop diuretics in combination with IV nitrates, and IV loop diuretics in combination with IV nesiritide.

Outcome Measures

The primary outcomes, measured during the index AHF hospitalization, were inpatient mortality, hospital length of stay (LOS), medical resource utilization, and total hospitalization costs. Resource utilization included proportions of patients with ≥1 use of 1) concomitant medications (angiotensin-converting enzyme inhibitors, angiotensin II blockers, aspirin, beta-blockers, clopidogrel, digoxin, diuretics [non-IV], hydralazine, IV morphine, vasodilating inotropes, vasopressor inotropes, warfarin), 2) diagnostic tests (angiocardiography, cardiac catheterization, chest x-ray, computerized tomography, echocardiogram, electrocardiogram, intravascular ultrasound, magnetic resonance imaging, multiple-gated acquisition scanning of the heart, nuclear myocardial perfusion scan, positron-emission tomographic scan, stress test), 3) selected surgeries or procedures (biventricular pacemaker or cardiac resynchronization, heart transplantation, implantable cardioverter-defibrillators, angioplasty, atherectomy, radiofrequency ablation, stent procedure, coronary artery bypass graft, ventricular assist device, valve surgery, ventricle reconstruction surgery), and 4) laboratory tests (basic metabolic panel, blood count, blood lipids, plasma B-type natriuretic peptide, comprehensive metabolic panel, glycohemoglobin, renal function, serum electrolytes, serum potassium concentration, therapeutic drug assay [digoxin], thyroid-stimulating hormone, thyroid function test, urinalysis). Costs reflect the actual costs to the hospital for the care provided and were calculated among a subset of hospitals with reported costs data.

A secondary outcome was HF rehospitalization rate occurring within 6 months and 1 year of index AHF hospitalization. HF rehospitalizations included all hospitalizations with a primary or secondary diagnosis for HF (ICD-9-CM 428.xx). Time from discharge to rehospitalization was measured in calendar months, because the exact day of the month is not provided for admissions or discharges in the HDD. Therefore, rehospitalization rates at 6 months and 1 year are within a precision range of ±1 month. As a sensitivity analysis, rehospitalization rates were calculated for those hospitalizations with AHF as the primary diagnosis only.

Statistical Analyses

Patients' demographic and clinical characteristics as well as treating hospital characteristics were assessed during the index hospitalization. The mean and SD were calculated for continuous