A novel strategy to reduce the readmission rates in congestive heart failure: intermittent empirical intravenous diuretics

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Improvements in the medical management of heart failure have changed the course of the disease. However, mortality rates, hospitalization rates, and treatment costs are not at desired levels. Diuretics have been widely used in the treatment of congestion in heart failure patients. The following case reports represent a special patient group treated and followed by cardiology clinic. Treatment approach of each case report has been tailored on an individual basis depending on the clinical course and hospitalization rates of patients. Authors have highlighted and discussed the common aspects and future perspectives of their cases in which post-discharge intermittent empirical intravenous diuretic administration dramatically improved the clinical status and readmission number due to decompensated congestive heart failure. This is a relatively new and promising approach, which has been thought to cease the recycle of diuretic resistance and silent increase of fluid congestion in patients with congestive heart failure and frequent hospitalization.
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Introduction

There have been significant improvements in the med-ical and surgical management of congestive heart fail-ure (CHF) patients. Despite all the advances, mortality rates are still high and frequent hospitalizations due to decompensation and subsequently increasing treatment costs continue to be an important problem. Orally taken diuretic therapy, especially loop diuretics, is widely used to treat the congestion but diuretic resistance develop-ment limits the efficacy of the treatment. When decom-pensation occurs, intravenous (i.v.) diuretic therapy is the preferred treatment choice [1,2]. Intravenous diuretic treatment strategy has been used to reduce hospitali-zations and to decongest the hemodynamically stable patients in an ambulatory setting [3–6], although there is a lack of guidance and specific recommendations. Herein, we describe three cases of CHF patients who require frequent hospitalizations due to decompensation and managed in a stable condition for long-terms with inter-mittent empirical intravenous diuretic (IEID) therapy.

Case reports

Case 1

This case report concerns a 69-year-old man with CHF. His medical history has given that he has had hyper-tension and normal coronary arteries proven by coro-nary angiography. He has no diabetes mellitus. He has also implantable cardioverter-defibrillator implantation. During the last year, he has been hospitalized due to decompensation of heart failure (HF) frequently in other medical centers. The patient was brought into the emer-gency department with 3 days of worsening shortness of breath and bilateral lower extremity swelling parox-ysmal nocturnal dyspnea, orthopnea and signs of S3 gallop, increased neck vein distension, pretibial edema, and rales up to two-thirds of lungs. He was considered to have New York Heart Association (NYHA) functional class IV. He had an ejection fraction of 15% with dilated left ventricular chambers and pulmonary artery pressure of 60 mmHg by echocardiographic examination and sinus tachycardia on electrocardiographic examination. Review of his medical records revealed that he had been dis-charged 2 weeks earlier on furosemide 40 mg once a day, metoprolol tartrate 25 mg twice a day, acetylsalicylic acid 81 mg once a day, spironolactone/hydrochlorothiazide 50/12.5 mg once a day, ramipril 2.5 mg once a day, digoxin 0.25 mg once a day. After 5 days of hospitalization, he was discharged with complete relief of HF signs and symp-toms. In addition to patient's current medication, he was also given to ivabradine 5 mg twice daily, and the dose of furosemide was increased to 40–80 mg daily. However, he was brought to emergency department almost in the same clinical situation and hospitalized two more times within the preceding 4 weeks. While discharging, patient was instructed to have empirical i.v. injection of furosem-ide 40 mg once in a week in any available medical center irrespective of HF symptoms. Thereafter, the patient has been followed up by policlinic visit with 3-month

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intervals without making any changes on latest oral medications and any deterioration on serum urea, creatinine, and electrolyte balance. He has still left ventricular ejection fraction of 15% and has been referred to a heart transplant program. He has never been hospitalized due to decompensation of HF during the 2 years follow-up period and has NYHA functional class II.

Case 2

This case relates an 81-year- old male patient who has been diagnosed with HF due to coronary artery disease. He also underwent percutaneous coronary intervention for left anterior descending and right coronary artery stenting after experiencing acute myocardial infarction 3 years ago. He had no diabetes mellitus and other sys-temic disease. His currents medications were digoxin 0.25 mg once a day, carvedilol 12.5 mg twice a day, iva-bradine 5 mg twice a day, clopidogrel 75 mg once a day, ramipril 2.5 mg once a day, furosemide 40 mg twice a day, spironolactone/hydrochlorothiazide 50/12.5 mg once a day, and atorvastatin 20 mg once a day. He was hos-pitalized 10 times in a year in our hospital during the follow-up period. Lastly, he presented to our emergency service with complaints of shortness of breath 5 days after previous discharge. ECG showed sinus tachycar-dia of 115 beats/min. His latest echocardiography results showed an ejection fraction of 30% with abnormal dias-tolic function, hypokinetic left ventricular wall motion, and mild mitral regurgitation. Physical examination was notable for respiratory crackles and a respiratory rate of 29 breaths per minute with low levels of peripheral oxy-gen saturation. His blood pressure was 170/90 mmHg. The chest radiograph was consistent with fluid overload. Clinical condition was diagnosed as acute pulmonary edema, and the patient was admitted to the coronary ICU where noninvasive ventilation support and i.v. nitrate infusion were started. After 5 days of hospitali-zation, he recovered of congestive symptoms. He also underwent coronary angiography to rule out coronary artery stenosis. There was no critical lesion in coronary angiography. Consequently, his HF therapy was mod-ified by uptitrating furosemide dose from 40 to 80 mg twice a day, and the patient was discharged home with a clinically good performance status. Additionally, he was recommended to use i.v. furosemide 40 mg every 3 days. After that, he has been hospitalized only 3 times dur-ing his follow-up of 1 year. Despite the administration of empirical i.v. diuretic doses, hypokalemia, and worsening of renal function requiring intervention have never been observed during the 3 months interval visits.

Case 3

A 73-old-male patient presented to our clinic with symptoms and signs of CHF. He had a history of coronary artery bypass grafting, and his recent coronary angi-ography revealed diffuse coronary stenosis in all three main native coronary arteries, which were unsuitable to revascularization. Electrocardiography was consistent with sinus tachycardia and echocardiography revealed an ejection fraction of 45% with abnormal diastolic dysfunction, mild mitral regurgitation, and pulmonary artery pressure of 45 mmHg. He was hospitalized six times last year due to decompensation of HF. In addition, there were 15 days between the last two hospitalizations. He was on acetylsalicylic acid 100 mg once a day, metoprolol tartrate 50 mg once a day, valsartan-hydrochlorothiazide 160/12.5 mg once a day, isosorbide mononitrate 60 mg once a day, ivabradine 5 mg twice a day, furosemide 40 mg twice a day, spironolactone/hydrochlorothiazide 50/12.5 mg once a day, ranolazine 375 mg twice a day, and atorvastatin 20 mg once a day treatment. He had no dia-betes mellitus. He was instructed to have empirically i.v. injection of furosemide 40 mg once in a week regardless of his signs and symptoms of HF. His functional status has decreased from NYHA class III-IV to NYHA class II. He was examined regularly for adherence to treatment with intervals of 3 months, clinical status and electrolyte imbalance. His ejection fraction remained unchanged. He has been on hemodynamically stable conditions, and he has not been hospitalized for decompensation of HF for 1 year.

Treatment protocols of IEID were tailored individually and patients were instructed to have i.v. diuretic injec-tion in primary health centers by general practitioners. All patients gave informed consent.

Clinical features and medications of the three patients are summarized in Table 1.

Discussion

The common features of our cases: (1) all patients had frequent hospitalizations due decompensation of CHF with repeating intervals of one week to utmost 1 month,
(2) number of hospitalizations dramatically decreased after IEID administration, (3) improvement in functional capacity of patients maintained during the follow period of IEID treatment in all three patients, and (4) none of the patients had serum electrolyte disturbances and worsening renal functions.

Despite the advances in medical therapy of HF over the past decades, repeated hospitalization still remains a significant burden in cardiovascular area. Although improvement in prognosis achieved by medical treatments, such as beta-blockers and angiotensin-converting enzyme inhibitors, diuretics has been the mainstay of therapy in HF to relieve the congestion and improve the symptoms [2]. Despite the widespread use of diuretics, there is a lack of guidance on how to best titrate these medications in chronic use and a substantial degree of uncertainty persists about the best way to utilize diuretics in patients with HF. Guidelines support the use of diuretics at the lowest clinically effective dose to maintain an euvolemic state but do not specify a diuretic strategy beyond that

Table 1 Clinical characteristics and medications of the patients

	Case 1	Case 2	Case 3
Age	69	81	73
Gender	Male	Male	Male
Etiology	Non-ischemic	Ischemic	Ischemic
ECG	Sinus tachycardia	Sinus tachycardia	Sinus tachycardia
LVEF (%)	15	30	45
Oral medications	Acetylsalicylic acid 81 mg 1 × 1 Digoxin 0.25 mg 1 × 1 Furosemide 40 mg 2 × 1 Ivabradine 5 mg 2 × 1 Metoprolol tartrate 25 mg 2 × 1 Ramipril 2.5 mg 1 × 1 Spironolactone Hctz 50/12.5 mg 1 × 1	Atorvastatin 20 mg 1 × 1 Carvedilol 12,5 mg 2 × 1 Clopidogrel 75 mg 1 × 1 Digoxin 0.25 mg 1 × 1 Furosemide 40 mg 2 × 1 Ivabradine 5 mg 2 × 1 Ramipril 2.5 mg 1 × 1 Spironolactone Hctz 50/12.5 mg 1 × 1	Acetylsalicylic acid 100 mg 1 × 1 Atorvastatin 20 mg 1 × 1 Furosemide 40 mg 2 × 1 Isosorbide mononitrate 60 mg 1 × 1 Ivabradine 5 mg 2 × 1 Metoprolol tartrate 50 mg 1 × 1 Ranolazine 375 mg 2 × 1 Spironolactone Hctz 50/12.5 mg 1 × 1 Valsartan Hctz 160/12.5 mg 1 × 1
Hospitalization frequency	Several times in previous years	At least 10 times in previous year	Six times in previous year
Empirical iv furosemide dose	40 mg once a week	40 mg every 3 days	40 mg once in a week
Follow-up without hospitalization	2 years	3 times hospitalization in the last year	1 year

HCTZ, hydrochlorothiazide; IV, intravenous; LVEF, left ventricular ejection fraction.

[1]. In outpatient clinical follow-up of patients with CHF, it is advised to increase the oral diuretic therapy [7,8]. The dose-response curve for loop diuretics which is called a sigmoidal curve[9] shifts downward and to the right in CHF, necessitating a higher starting dose in order to achieve the same level of sodium excretion [9,10]. On the other hand, i.v. loop diuretic therapy is the preferred method of treatment in acute decompensated CHF due to quicker mechanism of action [7,8]. It is advised to increase the frequency of administration rather than increasing the dose of drug concentration to achieve fur-ther diuresis [11].

Intravenous diuretic strategy has been used to reduce hospitalizations and to decongest the hemodynamically stable patients in an ambulatory setting. Administration of i.v. loop diuretics in an ambulatory setting has been used to reduce hospitalizations by countering the resist-ance to increased oral doses of loop diuretics. This strat-egy has been utilized by several centers to help reduce hospitalizations, specifically targeting those patients with volume overload mild decompensation that would only require one or two doses of i.v. diuretic to achieve euvolemia. Preliminary reported experiences so far have demonstrated that this as a safe and effective way to decongest hemodynamically stable patients and potentially reduce hospitalizations for HF and overall healthcare costs [3–5]. These outpatient HF units may, therefore, be useful to address those stable patients who appear to have diuretic resistance not surmountable by oral doses and just need some decongestion in order to respond to oral doses again [12]. It has been reported that rehospitalizations for HF are typically preceded by a gradual rise in ventricular filling pressures that begins 2 weeks in advance of detectable changes in weight or overt clinical symptoms [13]. Therefore, it is reasona-ble to commentate that IEID might have interrupted the silent increase in ventricular filling pressure and presumably volume overload in our patients before the development of clinical symptoms and signs. Individual approach, decreased hospitalization by time, patient base tailored therapy might have increased the patient compliance and resulted in improvement of clinical course of the patient. Intravenous injection of diuretics has also beneficial effects on the oral bioavailability of medicines, including diuretics, by decreasing gut edema.

Encouraging results of our case series regarding the clinical efficacy of outpatient IEID in patients with HF decompensation are consistent with the limited data available in the literature. The major differences of our cases than the previous reports are that patients are scheduled to administer i.v. furosemide empirically with a certain time of interval and irrespective of clinical symptoms or fluid retention. Successful clinical course of our patients without any renal deterioration ascertain the possible use of IEID in clinical practice of patients with frequently hospitalized due to decompensation of CHF. Likewise, Hebert K *et al*. [14] did not obtain blood chemistry panels prior to iv therapy and deemed this practice as safe in their population.

It is of note to mention that none of our presented cases had been using sacubitril which is an angiotensin recep-tor-neprilysin inhibitor and shown to reduce the hospitalization rates and diuretic needs in patients with CHF [15]. Likewise, a sodium-glucose co-transporter 2 inhibitor has also shown to result in greater electrolyte-free water clearance and, ultimately, in greater fluid depletion from the interstitial fluid space than from the circulation [16]. Irrespective of their beneficial effects on clinical course of patients HF, IEID treatment might be also useful in those with frequent hospitalization due to vol-ume overload and in whom already receiving angiotensin receptor-neprilysin inhibitor or sodium-glucose co-transporter 2 inhibitor.

The present clinical case studies suggest that the outpatient empirical iv furosemide injection represents a novel

strategy to be tested for reducing the readmission rates of patient with CHF effectively. These are the first case series evaluating the IEID treatment which is a promising but need to be confirmed by larger case series and studies. Individual cooperation and communication with patients is also essential issue to tailor the dosage, frequency, and adherence of patients to medical schedule and an important factor to achieve a steady euvolemic state. Although it is not possible to draw any firm conclusions from our case series, we believe that our case reports suggest the potential utility of outpatient IEID therapy in treating hemodynamically stable HF patients with hypervolemia to prevent repeated hospitalizations. Further clinical stud-ies evaluating the effectiveness of outpatient empirical iv furosemide or diuretics on readmission rates and fluid status optimization are warranted in patients with CHF. How this new level of approach might improve patients' quality of life and health cost by avoiding unnecessary hospitalizations remains to be elucidated as well.

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Conflicts of interests

There are no conflicts of interest.

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