European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Vasodilators in acute heart failure - evidence based on new studies

André M. Travessa, L. Menezes Falcão*

Centro Hospitalar Lisboa Norte, Lisbon, Portugal
Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

ARTICLE INFO

Keywords:
Acute heart failure
Vasodilators
Clinical trials
Mortality
Outcomes
Pharmacologic therapy

ABSTRACT

Acute heart failure (AHF) contributes largely to the worldwide burden of heart failure (HF) and is associated with high mortality, poor prognosis and high rehospitalization rate. The pharmacologic therapy of AHF includes diuretics and vasodilators, which are a keystone when fluid overload and congestion are present. However, vasodilators are mainly focused on controlling symptoms, and drugs that also improve long-term mortality and morbidity seem to be in high demand. In this review, we summarize the existing evidence on mortality benefits of IV vasodilators in AHF.

There is lack of evidence on the mortality benefits of IV vasodilators in AHF, as well as well-designed and large-scale trials for some of them. The existing trials on nitrates have conflicting results and are insufficient to establish definitive conclusions. Other vasodilators, such as enalaprilat, clevidipine, carperitide, and ularitide, have been evaluated only in a few trials assessing mortality. Levosimendan, nesititide and carperitide are approved by some regulatory agencies; however, data regarding mortality are also conflicting and large-scale post-marketing studies would be important. Serelaxin is a recent therapy with a novel mechanism of action and seemed to be promising; although serelaxin was safe and well tolerated in earlier trials, the results of a larger phase III trial failed to meet the primary endpoints of reduction in cardiovascular death at day 180 and reduction of worsening heart failure at day 5.

The absence of definitive mortality benefits and high-quality and large-scale data not allow firm conclusions to be drawn about the role of IV vasodilators in AHF. Well-designed studies are needed to clarify the role of these drugs in the long-term outcome of AHF, as well as new therapies entering the clinical investigation.

1. Introduction

Acute heart failure (AHF) is defined as the sudden onset of signs and symptoms of heart failure (HF) or the worsening of chronic HF manifestations, called acutely decompensated HF (ADHF) [1–4]. AHF may occur without recognized precipitant factors, but frequently one or more factors, such as infections or non-adherence to therapies, can be responsible [1].

Patients with AHF require immediate medical assistance and almost invariably need to be hospitalized [5,6]. In Europe, approximately 5% of all acute hospital admissions are associated with HF [7]. The median duration of AHF hospitalization ranges from 4 to 11 days; the in-hospital mortality ranges from 4% to 7% [2–4]. After discharge, the risk of rehospitalization or death in HF patients is high; the postdischarge mortality rate up to 3 months ranges from 7% to 11%, and about 25% of patients are readmitted within 3 months and two thirds within a year [2,8]. AHF represents a high proportion of HF-related health-care costs and an increasing major health problem. In fact, HF total cost is expected to increase from $31 billion in 2012 to $70 billion in the year 2030 in the United States (US) [9]. This equals approximately $244 for every US adult [10].

Intravenous (IV) loop diuretics are the mainstay in the AHF therapy [11]. Moreover, an IV vasodilator may also be used to decrease pulmonary edema, particularly in cases with persistent hypertension or manifestations despite administration of high doses of diuretics [12].

The ACCF/AHA guidelines suggest to consider the use of IV vasodilators as an adjuvant therapy to diuretics in patients with AHF, with the aim of relief of dyspnea [13,14]. The 2016 ESC guidelines suggest that IV vasodilators may be considered for improvement of symptoms in AHF patients with systolic blood pressure (SBP) above 90 mmHg and no symptoms of hypotension (Table 1) [1]. The two guidelines do not discriminate between nitroglycerin, nitroprusside, nesiritide and, in the ESC guidelines, isosorbide dinitrate (ISDN) [1,13,14]. Most of the data for these recommendations are provided from studies evaluating nesiritide; evidence on nitrates is limited to a few small, single-centre trials [1,13]. Although no IV vasodilators have been approved in the

* Corresponding author at: Centro Hospitalar Lisboa Norte, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal.
E-mail address: luis.falcao@chln.min-saude.pt (L. Menezes Falcão).

https://doi.org/10.1016/j.ejim.2018.02.020
Received 3 September 2017; Received in revised form 4 February 2018; Accepted 21 February 2018

Table 1
Clinical indications of IV vasodilators [1,13,14].

AHF
ESC guidelines • IV vasodilators should be considered for symptomatic relief in AHF with SBP > 90 mmHg (and without symptomatic hypotension); • In patients with hypertensive AHF, IV vasodilators should be considered as initial therapy to improve symptoms and reduce congestion. ACCF/AHA guidelines • If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with ADHF. Other indications • Hypertensive emergencies, angina/symptomatic coronary disease, hypertension following coronary bypass.

ADHD, acutely decompensated heart failure; AHF, acute heart failure, IV, intravenous; SBP, systolic blood pressure.

field of AHF since nesiritide in 2001 [15], some compounds have been evaluated in recent clinical trials.

In this paper we review the current role of IV nitrates and other traditional vasodilators for the treatment of AHF, as well as looking beyond the use of nesiritide and novel compounds under investigation, particularly focusing on mortality outcomes. A systematic search was performed in Pubmed from inception until August 2017 using the keyword heart failure and one of the following: nitrovasodilators, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, sodium nitroprusside (SNP), levosimendan, enalaprilat, clevidipine, serelaxin, RLX030, cinaciguat, nesiritide, carperitide, ularitide, TRV027, and nicorandil. The reference lists from identified articles were searched to identify any additional studies that may have been missed during the process, and the ClinicalTrials.gov database was searched using the above keywords to identify any finished but not yet published trials, as well as any trials that were still ongoing. We considered articles and entrances reporting trials whose results included mortality outcomes, and critically reviewed all of them.

2. Nitrovasodilators

As a class, IV nitrovasodilators provide a source of nitric oxide (NO). NO binds to soluble guanylate cyclase (GC), and consequently generate cyclic GMP (cGMP) that leads to vasodilatation [16].

There is a large experience in the use of nitrovasodilators in clinical practice and some small retrospective studies support it [17]. However, as shown below, nitrovasodilators have been evaluated in surprisingly few large, well-designed trials and high-quality data are lacking. Of the known trials, only a few were head-to-head comparisons of two vasodilators or similar agents, and randomized, controlled trials or even well-controlled observational studies are lacking, limiting conclusions of comparative efficacy. The absence of symptomatic, hemodynamic and long-term benefits and the absence of quality data to support firm conclusions were the findings of a recent meta-analysis [18]. The most important trials evaluating the use of IV nitrovasodilators for AHF are summarized in Table 2.

2.1. Nitroglycerin

IV nitroglycerin is a nitrovasodilator that was approved by the FDA for control of manifestations of HF in patients with myocardial infarction (MI) and also for treatment of angina pectoris refractory to sublingual nitroglycerin and beta-blockers [19]. Some clinical trials evaluated the benefit of IV nitroglycerin in the field of AHF [20,21], but only one assessed its effect on mortality. In this retrospective study [22], 430 consecutive patients with ADHF were randomized to receive neither diuretics nor nitroglycerin (group A), diuretics only (group B),

Table 2
Summary of most important trials evaluating IV nitrovasodilators in the field of AHF.

Trial (year)	IV nitrovasodilator	Characteristics	Number of patients	Interventions (number of patients)	Primary endpoints	Secondary endpoints
Aziz et al. (1995) [22]	Nitroglycerin	Retrospective cohort study	430	No diuretics/no nitrates (257) vs. diuretics only (127) vs. nitrates only (46)	Composite of all-cause mortality and ADHF readmission	Readmission, and mortality
Cotter et al. (1998) [28]	Isosorbide dinitrate	Prospective, randomized controlled trial	110	Isosorbide dinitrate (56) vs. furosemide (54)	Death in hospital, need for mechanical ventilation, and development of myocardial infarction	
Freund et al. (2011) [29]	Isosorbide dinitrate	Observational case series	136	Isosorbide dinitrate (25) vs. no isosorbide dinitrate (111)	Minimum SBP	Hospital length of stay, and in-hospital mortality
BA-HEF (2016) [30]	Isosorbide dinitrate	Prospective, multicentre, randomized double-blind trial	133	Hydralazine/isosorbide dinitrate (68) vs. placebo (65)	All-cause death or re-admission for HF	Change in symptoms of HF, change in SBP, functional status, and changes in markers of renal function
Mullens et al. (2008) [33]	Sodium nitroprusside	Observational case series	175	Sodium nitroprusside (78) vs. no sodium nitroprusside (97)	All-cause mortality, cardiac transplant, and first readmission for HF	Composite of all-cause mortality and cardiac transplant

ADHF, acutely decompensated heart failure; HF, heart failure; IV, intravenous; SBP, systolic blood pressure.