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HYDRALAZINE AND NITRATES IN THE TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION: A CLINICAL PERSPECTIVE

Muhammad Zubair Tariq[a], Ahmad Noeman[a], Saqib Shafi Sheikh[a]

Correspondence : Department of Cardiology, Punjab Institute of Cardiology, Lahore. Email: dr.zubayr@gmail.com
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Hydralazine and nitrates have long been parts of many studies for their potential benefits in heart failure with reduced ejection fraction (HFrEF). These agents have been used in combination and/or separately. Before the advent of ACEi these agents showed a significant improvement in symptoms, survival and repeated hospitalizations. Currently they are used alone or in combination with ACEi in addition to other heart failure medications.

Various studies have shown the clinical benefits of decreasing vascular resistance in patients with HFREF. Left ventricular function largely depends on preload and afterload. So by modifying these two with the above agents proved to be very helpful in HFrEF Isosorbide dinitrate is a venodilator and hydralazine is an arterial dilator. Nitrates act as NO donors, while hydralazine acts as an antioxidant through the reduction of NO consumption. One pivotal study on sodium nitroprusside in heart failure in patients with acute MI showed reduction in left ventricular filling pressures from 22.7±2.0 to 11.3±1.6 mm Hg and led to a modest increase in cardiac output [1]. In another study, sodium nitroprusside showed reduction in systemic vascular resistance and left ventricular filling pressure of 50% and 47% respectively and an increase in cardiac output of 56% [2]. So these beneficial effects on hemodynamics led to the studies with oral agents like isosorbide dinitrate and hydralazine. Massie et al studied the combination of hydralazine and ISDN (H-ISDN) in class III to IV heart failure patients in 1977, suggesting that simultaneously reducing afterload with hydralazine and preload with ISDN would result in a better response than with either drug alone. They found that H-ISDN caused reduction of both left ventricular filling pressure and systemic vascular resistance by 36% & 34% respectively and an increase in cardiac index by 58% [3].

LANDMARK TRIALS:

There were three pivotal trials of these agents which were V-HeFT I, V-HeFT II, A-HeFT. In 1986, Cohen et al published the first randomized controlled trial "Vasodilator Heart Failure Trial I (V-HeFT I)" that showed a survival benefit of the combination therapy in patients with heart failure [4]. The patients in this trial had impaired cardiac function, reduced exercise capacity while taking digoxin and diuretics. These patients were followed up for an average of 2.3 years. There was a 34% mortality-risk reduction at 2 years which became 36% by 3 years. V-HeFT II study led by Cohn compared enalapril with the combination of hydralazine and nitrates in 1991. The mortality rate was significantly lower in the enalapril arm (18%) than in the hydralazine and isosorbide dinitrate arm (25%), signifying a 28% reduction in the risk of mortality at 2 years of follow-up [5]. In African-American Heart Failure trial (A-HeFT trial) published in 2004 a fixed dose of isosorbide dinitrate and hydralazine plus optimal medical therapy was compared with optimal medical therapy alone in Black patients with advanced heart failure. This trial was terminated early due to significantly higher mortality rate in the placebo group (10.2% vs. 6.2%). The combination therapy (H-ISDN) resulted in 43% reduction in the rate of death from any cause and 33% relative reduction in the rate of first heart failure hospitalization and an improvement in the quality of life [6]. Therefore, the addition of a fixed dose of H-ISDN to standard therapy for heart failure including neurohormonal blockers is very efficacious and increases survival amongst Black patients with advanced heart failure.

DOSAGE AND COMMON ADVERSE EFFECTS:

The initial dose of fixed dose combination should be 1 tablet containing 37.5 mg of hydralazine hydrochloride and 20 mg of isosorbide dinitrate 3 times daily. The dose can be increased to 2 tablets 3 times daily for a total daily dose of 225 mg of hydralazine hydrochloride and 120 mg of isosorbide dinitrate. When these agents are used separately, both should be administered at least 3 times daily.

Initial low doses of the drugs given separately may be progressively increased to a goal similar to that achieved in the fixed-dose combination.

The most common problem with these agents is poor compliance and adherence due to large number of pills, frequency and high incidence of adverse reaction. Common adverse effects include headache, dizziness and gastrointestinal disturbances.

CURRENT GUIDELINES:

Currently there is a class 1 recommendation for use of H-ISDN to reduce morbidity and mortality in black patients with advanced HFrEF (NYHA III-IV) on optimal therapy with ACEi and B-blockers [6,7]. There is also a class IIa recommendation for patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insuffciency [8].

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