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Inotropic agents for the management of heart failure: Evidence from clinical trials

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ABSTRACT

Inotropes are the mainstay of treatment in heart failure, especially acute decompensated heart failure with reduced ejection fraction, cardiac output and organ dysfunction. They improve hemodynamics, organ perfusion and neurohumoral parameters but are often transient with increased side-effects. To provide an insight into the advantages offered by an inotrope over the other as well as its drawbacks, about 50 articles were reviewed from Elsevier, Lancet, Springer, JAMA, JAHA etc. Various heart failure trials studying the impact of inotropes on hemodynamic parameters, mortality, renal function and clinical outcomes conducted during a period between 1987- 2015 were selected. The subject population had a decreased ejection fraction or a higher NYHA (class II-IV). Various comparative trials showed that Levosimendan had better hemodynamics and renal efficacy compared to Dobutamine. However, there is an inconsistent report on effect of these drugs on mortality. In a few studies milrinone was found to be superior to Dobutamine in improving cardiac parameters, though in some Dobutamine was found to be similar to milrinone in improving cardiac index.There is a conflicting data on pros and cons of inotropes. Many studies comparing the effects of inotrope with placebo exist but those between different inotropes are a few and for a short period. For this, studies must be conducted in a larger population for a longer duration. In this review, we have assessed the current status of various inotropes including the novel agents and compared amongst their clinical outcomes, renal benefits and long-term effects on survival.

INTRODUCTION

Heart failure (HF) affects about 26 million people globally with an economic burden of $108 billion, a year [1]. In India, Cardiovascular diseases (CVD) were responsible for 24% deaths in the year 2014 and increased to 27% in 2016. There was a rise in prevalence of CVD from 25.7 million in 1990 to 54.5 million in 2016[2]. As per WHO Non Communicable Disease Indian profile, CVD accounted for 24% mortality in 2011 and 27% in 2018 [3, 4]. CVD leads to 17% of health expense in the US and is the major cause of death. Prevalence of HF in US approaches 5.7 million which accounts for one in every four deaths [5]. In Europe, CVD leads to 3.9 million deaths [6] Rise in prevalence of HF in 2016 as per European Society of Cardiology is 22% in Europe, 24% in North America and 32% in Africa [7].

Immediate management of HF is directed towards enhancement of hemodynamic parameters and organ perfusion, prevention of end-organ damage, providing symptomatic relief and decreasing the ICU stay [8]. Pharmacological treatments recommended in HF include diuretics, vasodilator, inotropes, vasopressors and thrombo-embolism prophylaxis.

I. INOTROPIC AGENTS: FACTS FROM TRIALS

Inotropes behold an important position in HF management. Heart Failure Society of America recommends use of I.V inotropes for symptomatic relief and to improve end-organ function in advanced HF with reduced left ventricular ejection fraction (LVEF) and low-output syndromes[9]. Continuous inotrope infusion is the preferred palliative measure in HF patients who are not willing for Mechanical Circulatory Support Devices [10]. It is recommended as an emergency measure in acute HF (AHF) with cardiogenic shock to increase the cardiac output (CO) [11]. Classification of inotropes are listed in table 1.

Table 1 : Commonly used ionotropic agents

INOTROPE	DRUGS
Sodium-potassium-ATPase Inhibitor	Digoxin
Catecholamine	Dobutamine, dopamine
PDE-3 Inhibitor	Milrinone, enoximone
Calcium sensitizer	Levosimendan, Pimobendan
Sodium-potassium-ATPase Inhibitor and SERCA activator	Istaroxime
Myosin activator	Omecamtiv mecarbil
SERCA activator	Gene transfer
Energy modulator	Etomoxir, pyruvate

Inotropes classified as per its mechanism of action and its examples are listed.

Sodium-potassium-ATPase inhibitor

The DIG trial revealed that even though there is no much difference in all-cause mortality and mortality due to cardiovascular (CV) causes, death from worsening HF was significantly low in digoxin group compared to placebo (p=0.06). These observations were confirmed with an ancillary trial. Mortality was found to be 115 (23.4%) and 116 (23.4 %) in digoxin and placebo group [12]. In RADIANCE TRIAL 23 patients in placebo and 4 in digoxin showed worsening HF (p<0.001). Increase in left ventricular end diastolic dimension i.e. LVEDD (p=0.09), left ventricular end systolic dimension i.e.LVESD (p=0.04), heart rate; HR (p=0.001), diastolic blood pressure; DBP (p=0.04), bodyweight (p<0.001) and decrease in LVEF (p=0.001) was found in placebo in comparison with digoxin maintenance group [13].

Catecholamine

In a study published in 1987, 20 patients with Congestive HF (CHF) were administered Dobutamine. Cardiac Index (CI) and CO increased at 60 min (P< 0.001) and at 72h (P<0.01). Pulmonary capillary wedge pressure (PCWP) reduced at both 60 min and 72h (p<0.05). Difference in stroke volume (SV), systolic blood pressure (SBP), DBP, right arterial pressure was not significant. LVEF improved at 60min (p< 0.02) [14]. In another study, 20 patients with severe CHF were given Dobutamine infusion. Exercise duration increased with Dobutamine (p<0.03 vs placebo, p<0.05 vs baseline). Dobutamine failed to demonstrate a significant effect in hemodynamic parameters. [15].

DAD - HF trial conducted from 2009 to 2010 compared the effects of low dose furosemide and low dose dopamine combination (LDFD) vs high dose furosemide (HDF) on diuresis and kidney function in 66 ADHF who received a bolus dose of furosemide followed by either HDF or LDFD. LDFD was equally effective as HDF but improved renal function. Insignificant changes in dyspnoea score was found in both the groups (p=0.575). [16] DAD - HF II trial compared the safety and efficacy of HDF versus LDFD or low-dose furosemide without dopamine infusion. Primary outcome such as CV mortality, all-cause mortality, hospital stay and hospitalisation for HF were not statistically significant. Dopamine infusion was not associated with any significant improvement [17]

PDE-3 inhibitor

In a study conducted in 1989 - 1990 in severe chronic HF patients, effect of oral milrinone on mortality was assessed. Compared to placebo, milrinone group showed an increase in mortality from all cause (p=0.038) and CV (p=0.016) respectively. Hospitalization was more in milrinone group (p=0.041) [18]. In a study conducted from 1997-1999, patients were randomised to receive a 48-hour infusion of either milrinone or placebo. Milrinone and placebo didn't differ significantly in duration of the hospital stay (p=0.71). Milrinone group showed atrial arrhythmia and hypotension more frequently than placebo (p=0.004 and p<0.001 respectively). Inpatient mortality (p=0.19), 60 day mortality (p=0.41) and readmission (p=0.92) differ insignificantly in both the groups. [19]

ESSENTIAL trial published in 2005, administered oral enoximone or placebo in chronic HF patients - US and Europe populations. There was no significant difference between the Enoximone cohorts in decreasing mortality (p=0.73). Distance covered on 6-minute walk test was 10m longer in Enoximone group (p=0.025) in American cohort and 1.5m in European cohort (p=0.82).[20] EMOTE trial was conducted in patients with

advanced or ultra-advanced HF, to determine if low dose Enoximone could wean patients off IV inotropic dependency. After 30 days placebo showed a higher wean rate (61.4%) than in the Enoximone group (51%), p=0.14. However, a statistical difference was attained after 60 days in Enoximone (p=0.016) [21].

Calcium sensitizer

In REVIVE I and II conducted from 2001 to 2004, ADHF patients who were given placebo showed worsening clinical outcomes than Levosimendan treated groups (p<0.029, p=0.015 respectively). B-type natriuretic peptide (BNP) levels improved in Levosimendan group at day 1 and 5 (both p<0.001). There was no statistical difference in NYHA, hospital stay and mortality between Levosimendan and placebo groups in both the trials [22]. In a study conducted by Hou ZQ *et al.*, Levosimendan decreased DBP (p<0.05), increased urine output (p<0.005) and eGFR at day 1, 3 and 7 (all p<0.005) compared to placebo [23]. Levosimendan improved LVEF (p=0.061), NYHA class (p=0.010), BNP (p=0.007), cystatin C (p=0.008) and decreased hospital stay (p=0.021) in patients with ADHF and renal impairment in comparison to placebo in a study published in 2017 [24]

In PICO trial, patients were randomized to receive either a Pimobendan 2.5 mg or 5mg daily or placebo. Compared to placebo, Pimobendan improved exercise capacity by 6% after six months of treatment. Pimobendan had no significant impact on patient's QOL or oxygen consumption. Mortality was 1.8 times greater in Pimobendan group [25]. The effect of Pimobendan on adverse cardiac events and physical activities with chronic HF was assessed in EPOCH study. There was a significant improvement in NYHA in Pimobendan compared with placebo (p=0.0013). LVEF improved in Pimobendan group (p=0.004). Serum atrial natriuretic peptide lowered in Pimobendan but increased in placebo after 52 weeks (p=0.0001) [26].

Sodium-potassium-ATPase inhibitor and SERCA activator

Istaroxime is an inotropic and lusitropic agent which inhibits sodium-potassium pump more effectively than digoxin. In HORIZON HF trial (2007), Cohort 1 received 0.5mcg/kg/min, cohort 2 a dose of 1mcg/kg/min and cohort 3 with 1.5mcg/kg/min of either Istaroxime or placebo. There was a significant decrease in PCWP at 6h in all 3 cohorts compared with placebo (all p<0.05). Lusitropic effects were evident by increased E-wave deceleration time in 3rd Istaroxime group (p=0.04) and rise in Ea velocity in 1st and 3rd Istaroxime group (both p=0.06) in comparison to placebo. QTc shortening was observed in all the 3 cohorts compared to placebo (p<0.0001) [27].

In a dose escalating study, Istaroxime was administered in 19 patients as 3 sequential cohorts. In the 1st cohort the total dose ranged from 0.3 to 3 mcg/kg, the 2nd cohort from 10 to 60 mcg/kg and the 3rd cohort from 100 to 300 mcg/kg. There was no significant decrease in BNP in either of the groups. Dose related QTC interval shortening was observed with Istaroxime treatment. The study could not conclude the hemodynamic effects [28].

Myosin activator

Omecamtiv mecarbil is the first selective cardiac myosin activator. They don't cause arrhythmias or tachycardia [29]. ATOMIC-AHF was done in acutely ill and hospitalized ADHF patients. Renal impairment and dyspnoea relief within 48h was similar to placebo. Patients in control group showed greater elevation in troponins compared to placebo but rehospitalisation was similar. Mortality was higher in control (33%) compared to placebo (2.6%) at 30 days but was lower at 180 days (12.5% vs 12.9%). All cause of death was CV and severe adverse events were similar in both the groups [30].

In COSMIC-HF Omecamtiv mecarbil reduced NTproBNP levels, significantly compared with placebo and also demonstrated its similarity in efficacy (EF, NTproBNP, LVEDD, LVESD and SV) in HF patients with ischaemic and non-ischaemic aetiology. There was insignificant elevation in troponin levels from baseline and was not associated with any ischemic events [31].

SERCA2a gene therapy

In CUPID, Nine patients with advanced HF obtained an intra-coronary infusion of Adeno-Associated virus type 1 (AAVI)/SERCA2a. After six months, an improvement from baseline in LV function (5 patients), QOL (5), NYHA (5) and a decrease in NT-proBNP (2) was noted. However, one patient showed worsening NT-proBNP, left ventricular end systolic volume and VO□ max. Patients were hospitalised due to unstable angina and uncontrolled diabetes mellitus but influenza and herpes zoster were also reported [32]. In CUPID 2 there was non-significant difference in rehospitalisation, improvement in NYHA, exercise tolerance and QOL and failed to meet safety and efficacy endpoints [33].

Energy modulator

A method to optimize cardiac energetics is to prevent fatty acid uptake via carmitine palmitoyltransferase 1 into mitochondria.

In a study published in 2000, HF patients were administered 80mg of etomoxir once daily for 3 months. During exercise, an increase in CO and LVEF (both p<0.01) and in SV (p<0.05) was noted. However, these effects were evident only within 3 months [34] In ERGO TRIAL, maximal exercise tolerance test and a 6-minute corridor walk test were found to be similar in etomoxir and placebo. Due to high liver transaminase level, the study was prematurely terminated [35]

The study conducted by Hermann HP *et al* assessed hemodynamic parameters after an intracoronary infusion of pyruvate. At highest pyruvate concentration, maximum rate of left ventricular iso-volumic pressure (LVISP) showed a 40% increase (p<0.05). HR and left ventricular end diastolic pressure decreased significantly (p<0.05 both). An increase in SVI, LVEF and mean arterial pressure (all p<0.05) was shown by pyruvate [36].In another study SV and CI improved from baseline (p<0.05 for both) while PCWP and HR decreased from baseline (p<0.05 for both) [37].

II. CLINICAL EFFECTS FROM COMPARATIVE TRIALS

A. Hemodynamics

In LIDO trial, hemodynamic improvement was higher in patients treated with Levosimendan (p=0.0222) compared with Dobutamine [38]. ADHF patients were randomized to receive either Levosimendan or Dobutamine in a study (2007-2009). The changes in PCWP, CI, SVR and CO from baselines showed significant difference between the groups (p=0.04, 0.01, 0.01, 0.01 respectively). However, there was insignificant difference in LVESD and SV[39].

In a study published in 2010, 136 patients were randomized to obtain Enoximone or Dobutamine or placebo. Improvements in CI and PCWP was more pronounced in Enoximone group ($p<0.05$). Right arterial pressure, SVR, PVR decreased significantly from baseline in the treatment groups compared to placebo. However, these differences were not significant among the interventional groups [40].

Another study compared milrinone vs Dobutamine in HF patients. CI ($p=0.0001$) and left ventricular systolic volume index ($p=0.0001$) was increased by milrinone and PCWP ($p=0.0001$), mean pulmonary artery pressure ($p=0.001$), mean arterial blood pressure ($p=0.0002$) was decreased whereas in Dobutamine, changes occurred at non clinical doses [41].

CI and SV ($p<0.05$) increased similarly by both milrinone and Dobutamine from baseline in a study conducted by Nicholas B *et al*. There was a decrease ($p<0.05$) in right ventricular end systolic volume and increase in right ventricular EF ($p<0.05$) from baseline. Compared to Dobutamine, milrinone reduced PCWP ($p<0.05$), pulmonary artery, peak systolic, end systolic and mean pressure ($p<0.05$) [42].

There was a similar increase in CI ($p<0.001$) by both milrinone and Dobutamine. Compared to Dobutamine, milrinone decreased left ventricular end diastolic pressure ($p<0.05$), right atrial pressure ($p<0.005$) and mean systemic arterial pressure ($p<0.05$) [43].

B. Mortality

In LIDO trial, 31day ($p= 0.049$) and 180 day mortality ($p= 0.027$) were higher in patients treated with Dobutamine than in Levosimendan group. Eight per cent of patients in Levosimendan group and 17% in Dobutamine group died within 31days and 26% and 38% at 180 days respectively [38] In SURVIVE (2003-2004) there was no statistical difference in 180 day mortality ($p= 0.4$) Death due to CV causes during 180 day was 157 in Levosimendan group and 171 in Dobutamine group ($p=0.33$). This could be due to the difference in history of HF between the groups or due to a different dosing regimen used in Dobutamine group compared with the LIDO trial [44].

C. Renal effects

In LIDO trial, Levosimendan group showed a significant decrease in serum creatinine compared with Dobutamine ($p=0.03$) [38]. In a study, eGFR improved in patients treated with Levosimendan after 24h and 72h ($p<0.001$) where as in Dobutamine group there was insignificant change [45]. Similarly in a study conducted in 2014, GFR was increased in Levosimendan group by 22% without any difference in Dobutamine group ($p= 0.012$). However, in Dobutamine group filtration fraction was reduced ($p=0.045$). Difference in renal oxygen extraction and renal blood flow, were not significant [46].

D. Clinical outcomes

In LIDO trial, hospital stay was decreased in Levosimendan group compared to Dobutamine group ($p=0.027$) [38] There was significant improvement in dyspnoea in Levosimendan group compared to Dobutamine ($p=0.04$) but not in NYHA class [39]. In SURVIVE trial, there was no significant changes in dyspnoea ($p=0.96$) and global assessment ($p>0.99$) at 24h and number of days alive and out of hospital ($p=0.3$) [44].

CONCLUSION

There is a conflicting data on benefits and risks associated with the use of inotropes. An inotrope may provide an acute clinical outcome but may reduce the long term survival. Some recommend their use for a shorter duration and stopped at the earliest whereas a few data suggest their use intermittently. Further trials are demanded to aid in the clinical selection of an inotrope. Many studies comparing the effects of inotrope with placebo exist but those between different inotropes are a few. Even in such studies clinical outcomes, renal benefits and long term effects on survival are not studied widely and more studies are warranted in this area. For this, studies must be conducted in a larger population for a longer duration.

CONFLICT OF INTEREST

None declared

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