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Original Research Article

Efficacy of Isosorbide dinitrate and Hydralazine combination in non ischemic dilated cardiomyopathy in a tribal based population at a tertiary care hospital

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ABSTRACT

Introduction: Non ischemic dilated cardiomyopathy is an important cause of heart failure and cardiovascular mortality. Numerous pharmacologic therapies have been applied from the ancient era for treatment. Some of them have shown improve morbidity. From various literatures it was concluded that combination therapy with H-ISDN in addition to conventional medicines are very effective in black population group. In our study we have tried to establish the efficacy of fixed dose drug combination (Hydralazine + Isosorbide dinitrate) to alleviation of heart failure symptoms and mortality benefit if any.
Materials and Methods: Patient in NYHA 3 or ambulatory class 4 were included in study. Total two hundred populations were included in the prospective study. One hundred patients were treated by conventional optimum medications for heart failure including ACE inhibitors, ARBs. One hundred patients were given ISDN+Hydralazine (fixed dose) in addition to conventional medicines.
Results: Mean age of study and controlled group was 62.5 years and 61.4 years respectively. Base line mean ejection fraction in control group was 33% and study group was 33%. After a mean one and half year follow up 61% of patient population achieved NYHA 2 in case group and 53% in control group. We assess the NT pro BNP level in both group of population at baseline and every six month interval. There is significant reduction in BNP level in study patients. 72% achieved below baseline cut off value for the age in control. In control population 51% achieved the estimated BNP value cut off for age.
Conclusion: Significant scope remains to improve the outcome for these patients through research related to use of H-ISDN in heart failure patients.

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1. Introduction

Despite the advances in pharmacotherapy for heart failure due to reduced left ventricular function mortality still remains high and many patients are hospitalized over time due to worsening of heart failure symptoms. There is some experimental evidence that vasoconstriction and Nitric oxide deficiency in the vasculature play a role in aggravation of symptoms of heart failure especially in black population.[1,2] Escalating dose of ISDN has been shown to increase symptoms free walking time. Development of tolerance is an important issue for continuation of long term ISDN. Combination of Hydralazine attenuates the development of hemodynamic tolerance to ISDN and increase the availability of NO in vasculature. Addition of combination ISDN plus Hydralazine in stable optimised medically treated patients improves NYHA class III, increase ejection fraction and improve mortality.[3,4] Retrospective analysis of published data suggested that this combination is more effective in black population group of heart failure patient.[5–9] Addition of combination ISDN+ Hydralazine in addition to state of the art of

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pharmacotherapy showed significant improvement of heart failure, delay in first hospitalisation due to heart failure and also mortality benefit.[10,11]

2. Materials and Methods

Patients attended in our hospital OPD with symptoms of heart failure screened for the study. Total two hundred patients were included in the prospective study. Patients in NYHA 3 or ambulatory class 4 were included in study. One hundred patients were treated by conventional optimum medications for heart failure including ACE inhibitors, ARBs. One hundred patients were given ISDN+Hydralazine (fixed dose) in addition to conventional medicines. Prospective follow up study was done for a period of one and half years. In control group six patients quit and two patients had died during our follow up study. In study group, four patients did not complete the full period of evaluation. Every patient follows up at three month interval and when required. Clinical data included dateof1st visit, Age, residence, race, sex, LVEF and associated co morbidities were recorded, Prescribing drug use, Laboratories values including NT pro BNP were measured in idiopathic cardiomyopathies with LVEF<40%. Other secondary cause of dilated cardiomyopathy was excluded by supplementary investigations. Echocardiography evaluation, functional class assessments, Subsequent gradation done at three month interval period. Every Patient was encouraged to strict adhere to medication and Telephonic communication with us when situation arises.

3. Results

One hundred patients were in controlled group and were recruited from patient attended at our Cardiology OPD as well as admitted in ward. Baseline investigation, Echocardiography, NYHA class, and recommended medicines including ACEI/ARBs were given to every patient. A master chart mentioning the date and Telephone number given to every patient. Patients were instructed to attend our OPD clinic at 3 month interval. During the follow up visit, we reassess the all mention parameters. In study group, one patient followed the same protocol with adding the medicine ISDN+Hydralazine in fixed dose combination. This population group are instructed to inform us if any suggestive symptoms and side effects of combination drugs such as headache, dizziness, and rash in face developed. Mean age for study group was 62.5 years. In study group, 66 % were male and remaining female Mean age of control group was 61.4 years and 62% patients were male. Six from study group and four from control group didn't the protocol as they were either quit or died. Mean ejection fraction in control group was 33% and study group was 33%. Median follow up was 18 months and 61% of patient population achieved NYHA 2 in study group and 53% in control group respectively. We assess the NT pro BNP level in both group of population at baseline and every six month interval. There is significant reduction in BNP level in study group. 72% patients of study group achieved below baseline cut off value. In control population, 51% achieved the estimated BNP value cut off for age.

Patients were instructed for hospitalisation when situation may arise. Index repeat hospitalisation was significantly reduced in study patients compared to conventional arm. Four patients from controlled arm and two patient from study arm died during the study period Though improve mortality occur with addition of ISDN+Hydralazine and conventional medication but not statistically significant ($p>0.05$)

4. Discussion

Till 1980s, treatment option for heart failure was limited to digitalis and diuretics. Although they were effective for symptomatic relief they did not give any mortality benefit. Search for more effective medication that modulates hemodynamics. Numerous physiological studies showed that dependence of ventricular function on vascular resistance and the drug that reduced systemic vascular resistance improve cardiac performance. Simultaneous use of fixed dose combination of two oral agents reduces the pre and after load result in better response than with either drug individually. It has been found that H-ISDN combination reduces left ventricular filling pressure by 36%, increases cardiac Index by 58% and reduces systemic vascular resistance by 34%.[12]Tolerance developed during long term use of ISDN that can be overcome by simultaneous Hydralazine. There is racial variation in prognosis of heart failure, black population are associated with worse outcome.[13–15] After adjustment of multiple variables black has higher all cause of mortality, pump failure, morbidity, combined death and heart failure hospitalisation. Not surprisingly approval of H + ISDN especially for blacks resulted in dialogues in both scientific and bioethical arenas. Proponents argued that although race is admittedly a poor marker of variation the benefits of the drug in blacks were too great to ignore. Nitric oxide is an important mediator of wide range of process including maintenance of vascular tone, myocardial hypertrophy and remodelling and maintenance of cellular redox balance.[16–18] [Data suggested that tribal based black population have difference in Nitric oxide hemostasis and impairment of NO mediated cardiovascular effect compared to white.[19,20] As ISDN is a NO donor and Hydralazine has antioxidant property that helps to prevent NO degradation combination treatment responsible for preferential treatment benefit in tribal based black population. Black appears to have worse impairment in NO mediated mechanism which may explain potential but unproven race related difference in heart failure out come and response to therapy. Genetic heterogeneity in

endothelial NO synthatase might account for the response to H-ISDN. However there is no significant survival benefit and quality of life over gender difference detected in our study population.

5. Conclusion

Although there are many benefit of H-ISDN combination in heart failure patient a number of unanswered questions ranging from efficacy and mechanism of action to defining optimal patient population potential remains for further to criticise the universal acceptance. In our study, we select the tribal based population to establish the previous records. Significant opportunity remains to improve the therapy for these patients through research related to use of H-ISDN in heart failure patients.

6. Source of Funding

None.

7. Conflict of Interest

None.

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