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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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A B S T R A C T

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 only morbidity benefit. Pauci number has definite mortality benefit. They have diverse mode of action, side effects, cost, drug interaction, tolerance. But here one size does not fit for all. Most of the medicines are costly. More than that they are not equally effective in all groups of patient. This racial difference in efficacy of medicines make it an important cause of treatment failure. 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. Though cheap objective of the study resolved, their remains some unanswered question which may possibly achieve in future to establish the long term benefit.

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. 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, increase ejection fraction, mortality benefit also detected though not statistically significant in our study. Retrospective analysis of published data suggested that this combination is more effective in black population group of heart failure patient. Addition of combination ISDN+HYDRALAZINE in addition to state of the art of pharmacotherapy showed significant improvement of heart failure, delay in first hospitalisation due to heart failure and also mortality benefit.

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MATERIALS AND METHODS

Patients attended in our hospital OPD with symptoms of heart failure screened for the study. Total two hundred populations were included in the study hundred patients were treated by conventional optimum medications for heart failure including ACE inhibitors, ARBs. 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 year. 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, associated co morbidities, LVEF, Prescribing drug use, Laboratories values including pro bnp our study only idiopathic cardiomyopathies with LVEF<40% included. 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.

RESULTS

In our study population control group was made with hundred patient populations. They are recruited from patient attend at

our OPD as well as admitted in our 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 case group of 100 patients population we follow 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 case group was 62.5 yrs. Out of 100 patient population 66 was male, 34 was female. Mean age of control group was 61.4 yrs at Presentation. Male was 62 and female was 38 in number . Six from case group as four from control group not completed the study as they were either quit or died. Mean ejection fraction in control group was 33% and case group was 33%. Pt in NYHA 3 or ambulatory class 4 were included in study.

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 six month interval. There is significant reduction in bnp level in case group. 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.

Both population group were instructed for hospitalisation when situation may arise. Index repeat hospitalisation was significantly reduced in case group compared to control group. During our study period four patient had died in control group and Two in case group. Though mortality benefit occur it was not statistically significant.

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. The search for more effective options lead to strategies that modulate 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%. Tolerance developed during long term ISDN use can be overcome by simultaneous Hydralazine use.There is racial variation in prognosis of heart failure, black population are associated with worse out come. 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. Data suggested that tribal based black population have difference in Nitric oxide hemostasis and impairment of NO mediated cardiovascular effect compared to white. 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.

CONCLUSION

Although there are many benefit of H-ISDN combination in heart failure patient a number of unanswered question 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.

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