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RANDOMISED OPEN TRIAL COMPARING THE EFFECT OF DAPAGLIFLOZIN ON C-REACTIVE PROTEIN AND EJECTION FRACTION IN HEART FAILURE PATIENTS

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ABSTRACT

Aim: To study the effect of dapagliflozin on C - reactive protein and Ejection fraction in heart failure patients. **Methodology:** It is **a** randomised open trial that is conducted to check the effect of dapagliflozin on C - reactive protein and ejection fraction .we randomly divided selected subjects into 2 groups that are treatment group and control group. Dapagliflozin has been given as an add-on therapy to the treatment group. We collected initial C - reactive protein and Ejection fraction before initiation of treatment for both treatment and control group and this value is compared with the values that are collected after treatment for both control and treatment group. **Result:** C - reactive protein before and after treatment has been found to be -13.13 and the standard deviation of the difference is equal to 2.376 after calculating p value it has been found to be 0.000025 which is less than the critical p value of 0.001 so we can concluded that reduction in mean C-reactive protein is more significant it has been found that the difference of mean ejection fraction before and after treatment with dapagliflozin is 10.1 and Standard deviation is 1.107 after calculating p value it has been found that p value is less than critical p value. **Conclusion:** It has been observed in both diabetic and non-diabetic patients taking dapagliflozin C - reactive protein and Ejection fraction has been improved more effectively in the treatment group. This formulation is expected to have an increased bioavailability of Maraviroc. The tablets are prepared by direct compression method using low-density polymers such as HPMC K100M, Carbopol 940, and Xanthum Gum. Sodium bicarbonate and citric acid are used as effervescence agents.

INTRODUCTION: Heart failure can be defined as the inability of a heart to produce an efficient amount of cardiac output that is necessary to meet the requirements of different body parts. Systolic dysfunction and diastolic dysfunction are the two kinds of heart failure.

C-REACTIVE PROTEIN: CRP gets its name from its propensity to precipitate streptococcus pneumonia c-polysaccharide.in the mid-1990 assay of C-Reactive Protein shown us that it is having greater sensitivity and revealed that when there is an increase in the C-Reactive Protein value then indicates that there is an increase in the risk of coronary heart failure. The clinical use of C - reactive protein has been ignored for more than 30 years. C - reactive protein is a part of nonspecific acute phase reactant whose value is increased during inflammation, infections, and also during certain tissue damage. C -

reactive protein test can be performed directly through commercially available automatically operated C - reactive protein assay or directly by using C - reactive protein as its reagent. C - reactive protein is the most important biochemical marker that is used for diagnosing organic disease, a certain type of inflammation and infection, and also a certain type of infection in immunocompromised patients.(3)

ROLES OF C-REACTIVE PROTEIN IN CARDIOVASCULAR DISEASES: The main risk factor for heart failure is atherosclerosis. Atherosclerosis is the complex inflammatory process triggered by lipid presence in the vascular wall, causing interaction of vascular walls, inflammatory cells and lipoproteins. As a result, adhesion molecules, cytokines are released and acute-phase reactants eventually increase. Acute reactants include fibrinogen, ceruloplasm, C-reagent protein, and so on. The levels of a protein called acute-phase protein in the plasma are used to detect these acute-phase reactants. The most significant acute phase reactant is C-reactive protein, which is created by the liver in response to elevated IL-6 levels.. C-Reactive Protein is the sensitive marker that used to denote atherosclerosis that influences the vascular vulnerability to several mechanisms such as increasing expression of adhesion molecule, altering LDL ingestions by macrophages, decreasing endothelial bioactivity of nitric oxide, etc. increase in the levels of CRP in the blood is used to denote the risk of occurrence of MI, stroke, PAD, and cardiac arrest.

As CRP is the most potential biomarker that is capable of detecting independently potential risk of cardiac disorders so it is called High sensitive C - reactive protein (hs CRP).(11) As a result, the levels of High Sensitivity-C-Reactive Protein are used to classify cardiovascular disorders divided into 3 types. Low risk- hs-CRP <1 mg/L, Moderate risk-hs-CRP>1-3 mg/l, High risk - hs-CRP>3 mg/l

ATHEROSCLEROSIS: Atherosclerosis means an intimacy of the arteries and a build-up of fat and it is from Greek origin. The plaque's centre, surrounded by a fibrous crown, contains fatty material. There are two parts of atherosclerosis: atherosis (fats with numerous macrophages) and sclerosis (fat accumulation without macrophages) (4)

ROLE OF C-REACTIVE PROTEIN IN DEVELOPING ATHEROSCLEROSIS: In 1982, it was found that C-reactive protein specifically bound to LDL and VLDL in atherosclerotic plaques, suggesting that it may have proatherogenic qualities. Inflammatory mechanisms are involved in all stages of atherosclerosis, from the initial recruitment of circulating leukocytes to the artery wall to the rupture of unstable plaques that results in clinical symptoms. C-reactive protein may have an impact on procedures such as complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid buildup, and thrombosis throughout each of these steps. In atherosclerotic lesions, particularly in the vascular intima, it is made up of monocytes, monocyte-derived macrophages, and lipoproteins. Atherosclerosis development is directly impacted by this localisation. The direct pro-atherogenic effects of C-reactive protein penetrate vascular smooth muscle in addition to the endothelium. It performs the following functions: *C-reactive protein amplifies and enables innate immunity through the activation of conventional complementary system pathways. This process has been associated with chronic heart disease starting and advancing. *C-Reactive Protein increases the absorption of LDL macrophages and increases the capacity of macrophages to form foam cells. It also binds the LDL phosphocholine oxidised. *Endothelial NO synthase expression in ECs is inhibited by C-reactive protein. Reduced platelet aggregation, smooth muscles cell proliferation and vasoconstriction are all anti-atherogenic action NO. *C-Reactive Protein stimulates the secretion of macrophages to the factor tissue, a powerful procoagulant that can produce diffused intravascular coagulation. *C-Reactive Protein causes ECs to produce more adhesion molecules, which attract monocytes to the injury site.

EJECTION FRACTION: In the process of Supplying oxygenated blood and also receiving deoxygenated blood from different parts of the body heart contract and relax in a

simultaneously .when the heart contracts blood is ejected from the ventricles and when the heart relaxes ventricles are refilled.

Ejection fraction is defined as the percentage of blood pumped out from the filled ventricle during each heartbeat

EF= SV/EDV=EDV-ESV/EDV

Where EF = Ejection fraction, SV= stroke volume, EDV= end-diastolic volume, ESV= End stroke volume

MATERIALS AND METHODS: *The Durgabai Deshmukh Hospital's institutional ethics committee approved this study. This 6-month study was carried out at Durgabai Deshmukh Hospital's cardiology department, which has 250 beds. * A study was carried out to compare CRP and EF in control and treatment group before and after treatment with dapagligflozin in heart failure patients. Patients from the age of 18 was selected and patients with EF less or equal to 40% was selected. Pregnant and patients with any kind of infections was excluded from the study.

RESULTS AND DISCUSSION: The purpose of this study is to see how dapagliflozin therapy affects the responses of heart failure patients. C - reactive protein levels and ejection fraction levels are compared to other treatments. For this purpose, 40 heart failure patients were recruited from durgabhai deshmukh hospital, Hyderabad, of whom 20 subjects referred as treatment group received treatment with dapagliflozin while other 20 subjects considered as control group were not treated with other therapies without dapagliflozin. This investigation was carried out at the Durgabai Deshmukh Hospital under the direction of a skilled physician. 40 patients were the subject of an extensive investigation that lasted six months, and the findings were interpreted. Each patient underwent routine observations during which their vital signs, lab results, and medication charts were evaluated based on how long they had been hospitalised. Each patient's recorded data was entered into our data collecting form, which was created to match the needs of our study. Based on our study's goal, the results are shown below utilising pie charts and histograms. Demographic data on gender, age, and social habits such as smoking and alcohol consumption were collected from all 40 patients and the distribution of these cases among the treatment and control group with regard to these variables was described. Gender wise distribution revealed higher preponderance of males in the treatment group versus the control group. Overall, 65% of males were observed (26/40) indicating that incidence of heart failure is more in males. Males seem to pose increased risk for heart failures as compared to females. The test statistic T equals -5.5258. The difference of means before and after treatment is -13.13 and the statistic is computed using the standard deviation of the difference, S', which equals 2.376. The p-value equals 0.000025 which is lesser than the critical p value of 0.001. The difference is significant at 99% confidence levels. After treatment with dapagliflozin, patients' mean C-reactive protein levels decreased significantly. In both treatment and control group, significant percentage of patients showed reduced C - reactive protein levels as therapy response. Overall, patients with reduced C - reactive protein levels were prominent in treatment group. The test statistic T equals -4.1002. The difference of means before and after treatment is -16.05 and The S' equals 3.914, the standard deviation of the difference is used to calculate the statistic The p-value equals **0.002676.** The drop in mean C-Reactive Protein levels in patients in the control group following therapy with dapagliflozin was equally significant Although both the groups revealed significant reduction in mean C - reactive protein levels after therapy as compared to before therapy, the magnitude of reduction was higher in treatment group with dapagliflozin. The test statistic T equals **9.1225**. The difference of mean ejection fraction before and after treatment with dapagliflozin is10.1 and the statistic is calculated using the standard deviation of the difference, S' = 1.107. The p-value equals **2.262e-8,** which is lesser than the critical p value of 0.001. The difference is significant at 99% confidence levels. The increase in mean ejection fraction levels in patients after treatment with dapagliflozin is highly significant. The test statistic T equals **7.5165.**

Table 1: Gender wise distribution of heart failure patients among treatment group and control group

	Male		Female		Total
	No. of subjects	%	No. of subjects	%	
Treatment group	14	70%	6	30%	20
Control group	12	60%	8	40%	20

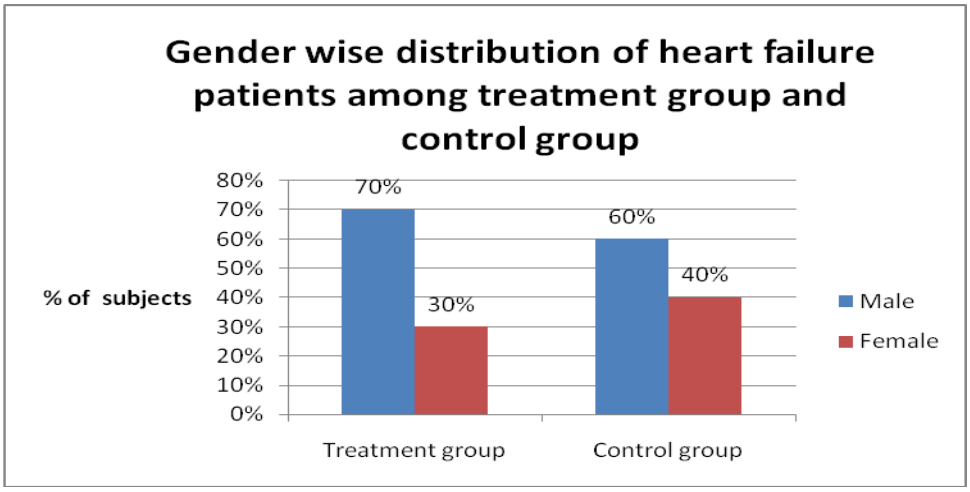


Table 2: a) Comparison of C - reactive protein values of heart failure patients in the treatment group before and after the treatment with dapagliflozin

CRP level(10mg/L)	Before treatment		After treatment	
	no. of individuals	%	no. of individuals	%
< 10	13	65%	16	80%
>10	7	35%	4	20%

Table 3: a) Mean C - reactive protein levels in heart failure patients in treatment group before and after the treatment with dapagliflozin

	No. of individuals	Mean	SD
Before treatment	20	19.62	15.473
After treatment	20	6.49	5.245

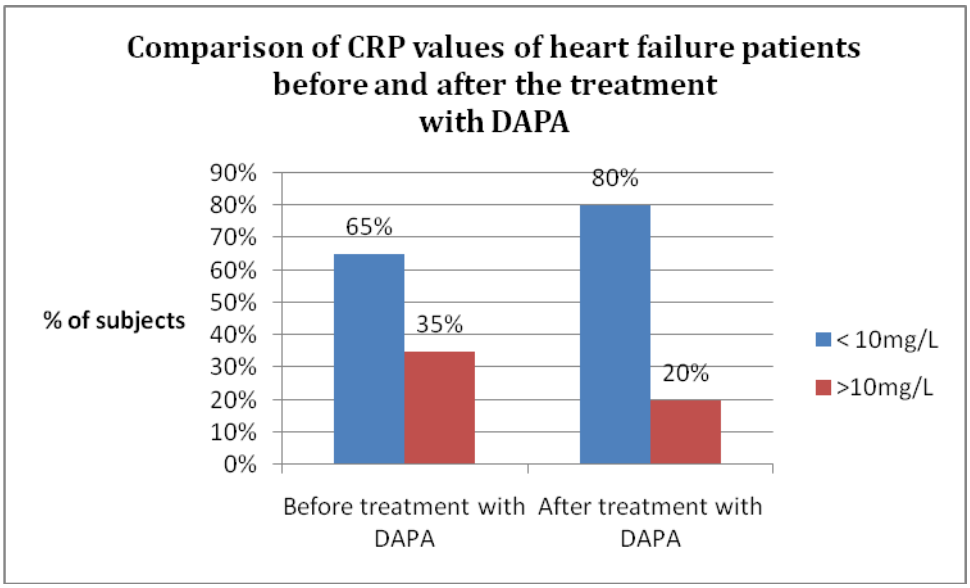


Table 5: b) Mean C - reactive protein levels in heart failure patients in control group before and after the treatment without Dapagliflozin

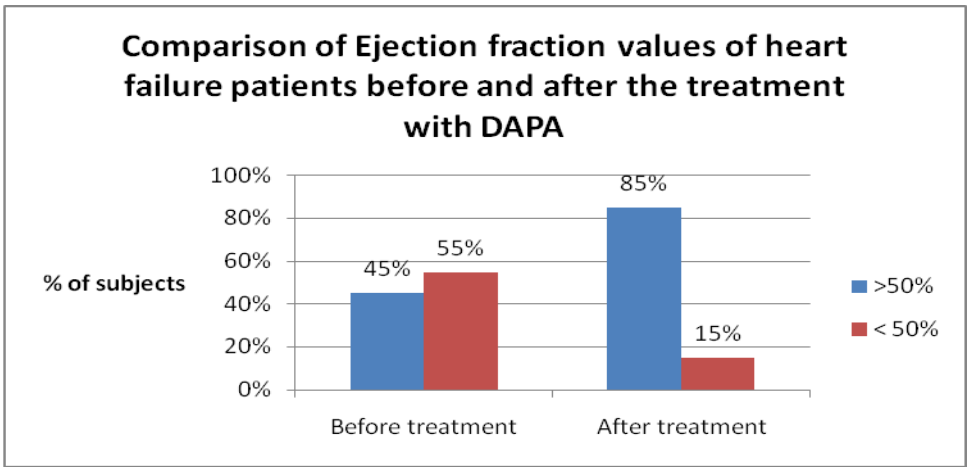
	No. of individuals	Mean	SD
Before treatment	20	29.1	20.74
After treatment	20	13.05	9.67

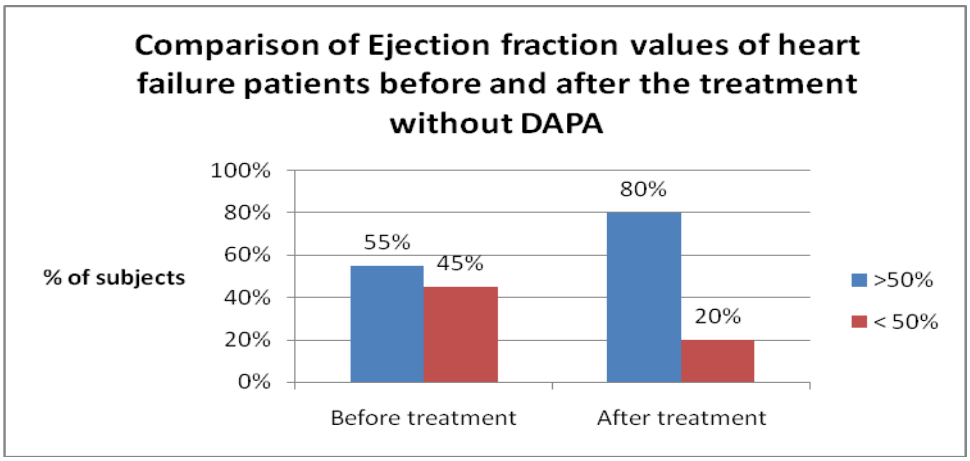
Table 4: a) Comparison of Ejection fraction values of heart failure patients in the treatment group before and after the treatment with dapagliflozin.

	Before treatment		After treatment	
Ejection fraction	**no. of individuals**	%	**no. of individuals**	%
>50%	9	45%	17	85%
< 50%	11	55%	3	15%

Table 4: b) Comparison of Ejection fraction values of heart failure patients in control group before and after the treatment without dapagliflozin

	Before treatment		After treatment	
Ejection fraction	**no. of individuals**	%	**no. of individuals**	%
>50%	11	55%	16	80%
< 50%	9	45%	4	20%





The increase in the proportion of patients with elevated Ejection Fraction is prominent in both groups after the treatment.

Table 5: a) Mean Ejection fraction levels in heart failure patients before and after the treatment with dapagliflozin

	No. of individuals	Mean	SD
Before treatment	20	50.8	11.076
After treatment	20	60.9	7.275

Table 5: b) Mean Ejection fraction levels in heart failure patients in the control group before and after the treatment without dapagliflozin

	No. of individuals	Mean	SD
Before treatment	20	51.3	11.16
After treatment	20	59.7	8.23

The difference of mean ejection fraction before and after treatment without dapagliflozin is 8.4 and the statistic is calculated using the standard deviation of the difference, S' = 1.118. The p-value equals **0.00003629**, which is lesser than the critical p value of 0.001. The difference is significant at 99% confidence levels. The results revealed significant reduction in C - reactive protein levels and increase in Ejection fraction in heart failure patients after the treatment with dapagliflozin as compared to other therapies. Also the duration of response was earlier in dapagliflozin treated than without dapagliflozin. These observations indicate that dapagliflozin can effectively improve the treatment outcomes when administered along with standard treatment. The findings need to be explored on large scale in a systemic manner considering other outcome variables and differential risk factors.

SUMMARY

A total of 40 individual with or without diabetics has been selected of that 20 individuals are treated with the dapagliflozin

* Clinical presentation, stages of heart failure, Treatment given is compared in both treatment group and control group * Initial C - reactive protein values has been checked before initiation of treatment for both treatment group and control group *It has been found that difference before and after treatment has been found to be -13.13 and the standard deviation of the difference is equal to 2.376 after calculating p value it has Been found to be 0.000025 which is less than the critical p value of 0.001 so we can concluded that reduction in mean C-reactive protein is more significant

*initial Ejection Fraction has been calculated before and after initiating treatment *It has been found that the difference of mean ejection fraction before and after treatment with dapagliflozin is 10.1 and Standard deviation is 1.107 after calculating p value it has been found that p value is less than critical p value * It is concluded that mean Ejection fraction in patients after treatment with dapagliflozin is highly significant.

CONCLUSION:

Both diabetic and non-diabetic patients have been selected. Cases are compared based on age, social status, duration of treatment among treatment and control group. It is concluded that C-Reactive Protein values, ejection fraction, length of hospital stay, worsening of heart failure have been decreased in patients receiving dapagliflozin compared to the group not receiving dapagliflozin as an add on therapy

Ethics and consent: Throughout the course of the study, the AHA/ASA standards were upheld. All relevant and necessary information was acquired from health records, lab results, prescriptions, and patient interviews.

Conflicts of Interest: None

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