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STUDY OF THE EFFICACY AND SAFETY OF IV CARNITINE IN CHF

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ABSTRACT

Congestive Heart Failure (CHF) is one of the most prevalent public health problem of today. CHF is not a disease but a condition that occurs when the heart is unable to pump enough blood to meet the needs of body's tissues. Deficient myocardial Carnitine levels are also involved in the pathogenesis of CHF. Various inotropic drugs, diuretics and vasodilators used in treatment improved the condition of CHF patients to some extent. In this present study, efficacy and safety of Carnitine in CHF is evaluated. It is observed that administration of 2gms of IV L-Carnitine/day improved the condition of CHF patients with beneficial effects characterized by significantly increasing Ejection fraction ($P<0.001$). It stimulates the cardiac metabolism and increases the coronary blood flow and decreases ventricular dilation and reduces triglyceride levels significantly ($p<0.001$).

KEY WORDS: **CHF, L-Carnitine , Ejection fraction, Triglycerides.**

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INTRODUCTION

CHF is a state in which the heart fails to maintain an adequate circulation of blood for the needs of the body despite a satisfactory filling pressure. About 2,50,000 people die of heart failure each year. For people over 65 years, it is number one cause of death. About two thirds survive the year of diagnosis and those who survive appear to function well. Women have a better survival rate than men.[1]

CAUSES OF CONGESTIVE HEART FAILURE

Common causes for CHF are ischemic heart disease, hypertension, cardiomyopathies, diabetes mellitus, valvular heart disease, and rheumatic myocarditis, alcoholism and emphysema. Precipitating causes for CHF are arrhythmias, pulmonary embolism, anemia, thyrotoxicosis and pregnancy. Physical over exertion, excessive environmental heat or humidity and emotional crisis all may precipitate heart failure in patients with heart disease who were previously compensated[2].

PATHOPHYSIOLOGY

Congestive heart failure is a gradually developing inability of the heart to pump sufficient blood to satisfy the needs of body, i.e. it fails to function as an efficient pump. There is a depression of the Starling's curve relating cardiac performance to ventricular filling pressure. The fundamental cause is unknown, but the biochemical defect is an ineffective conversion of chemical energy to mechanical work. This results in an inadequate cardiac output causing breathlessness on exertion or even at rest, chronic venous congestion, salt and water retention, fatigue, confusion and renal failure[3]. In congestive heart failure, cardiac output (co) is decreased due to decreased myocardial contractility. Cardiac output depends on the heart rate (HR) and the volume of blood that is ejected with each beat i.e. the stroke volume (SV). Their relation is expressed by the equation:

$$CO = HR \times SV$$

There are three factors that regulate the SV namely preload, after load and contractility[3].

In early stage of heart failure the compensatory mechanisms are activated to maintain cardiac output. These mechanisms are normally reserved for cardiovascular stress and exercise. In advanced heart failure the heart has no functional reserve and decreased perfusion accounts for the symptoms even at rest and the heart becomes decompensate and dilated[3].

SYMPTOMS

Cardinal symptoms of congestive heart failure are dyspnea, orthopnea, paroxysmal nocturnal dyspnea, Cheyne-stokes respiration, fatigue, weakness, abdominal symptoms like anorexia, nausea and abdominal pain and cerebral symptoms like cerebral arteriosclerosis, reduced cerebral perfusion, and arterial hypoxemia. There may be confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety[2].

PHYSICAL FINDINGS

In moderate heart failure, the patients appear to be in no distress at rest except that he or she may be uncomfortable when lying flat for more than a few minutes. . In more severe heart failure, the pulse pressure may be diminished and the diastolic arterial pressure is elevated as a consequence of generalized vasoconstriction[2]. In Acute heart failure, hypertension may be prominent. There may be cyanosis of the lips and nail beds and sinus tachycardia. The patient may insist on sitting upright. Systemic venous pressure is abnormally elevated in heart failure and can be recognized by observing the extent of distention of the jugular veins[2]. Third and fourth heart sounds are often audible but are not specific for heart failure. Pulsus alternans is present. It is a sign of severe heart failure[2]. Other findings are pulmonary rales, cardiac edema, hydrothorax, ascites, hepatomegaly, jaundice, and cardiac cachexia etc[2].

COMPLICATIONS[2].

- Cardiac arrhythmias, occur due to sympathoadrenal activation, and Hypokalaemia.
- Deep venous thrombosis occurs due to immobility, and hypokinetic flow.
- Thromboembolism occurs due to chamber dilatation, hypokinetic flow, and atrial arrhythmias.
- Vital organ failure occurs due to reduced cardiac output, Hypotension.
- Sudden death may occur due to sympathoaderenal activation and hypokalemia.

DRUGS USED FOR CHF[8]

- ACE inhibitors, vasodilators, ionotropic Drugs, Digitalis, Betablockers, Anti-Clotting Drugs, and Anti-Arrhythmic Drugs and diuretics.
- Drugs for symptom relief.

L-CARNITINE

L-Carnitine is a quaternary ammonium compound and is an essential factor in fatty acid metabolism. It is also called vitamin B_T. In humans, Carnitine is synthesized largely in liver and kidney. Though, biosynthesized in the body, L-Carnitine availability largely depends on dietary intake. In normal healthy and well-fed adult, this requirement is 100-300mg/day. Red meat and dairy products are good sources of L-Carnitine, while vegetables in general have low Carnitine levels[4]. Heart and skeletal muscles get most of their energy needs by oxidizing fatty acids for which availability of L-Carnitine is very essential. Since, heart relies heavily on Carnitine for its energy requirement it is said to be the vitamin of heart muscles. When the heart is offered both glucose and high concentrations of fatty acids, fatty acids are the preferred substrates even in the presence of insulin[4]. Derivatives of Carnitine exists in the form of two sterioisomers, Dextro(D) and Levo(L) forms. Only the L-form is biologically active. D-form is completely biologically inactive. L-Carnitine plays an important role in β-oxidation of fatty acid. It serves as a transport system for long chain fatty acid transport across the inner mitochondrial membrane for energy production[4]. In the bioavailability study of 15 healthy adult males, Carnitine injection administered as a slow 3min bolus intravenous injection at a dose of 20mg/Kg. 76% of free L-Carnitine is eliminated in the urine.

PHARMACODYNAMICS

Effect on Lipid metabolism: Loss of Carnitine leads to the accumulation of triglycerols in the heart. Carnitine may protect the ischemic heart by preventing the accumulation of lipid intermediates. Carnitine treatment increases urinary excretion of long and short chain Carnitine esters. Carnitine significantly reduces the total cholesterol and triglycerides levels. Carnitine transfers long chain fatty acids from the cytoplasm into the mitochondria,permitting β-oxidation and producing energy in the form of ATP[5]. Anti-anginal Effect: Carnitine improves exercise tolerance in patients with effort Angina and decreases episodes of Angina pectoris and reduces the ST segment depression[6]. Effect on ventricular remodeling: Carnitine modulates ventricular dilatation by limiting the infarct size and it reduces Lt ventricular wall stress, end diastolic and systolic volume and reduces necrotic area measured by CPK(MB) release[7]. Effect on myocardial contractility: Experimental studies on the effect of Carnitine treatment on ischemic heart reported several haemodynamic improvements such as Lt ventricular pressure, mean aortic pressure, Lt ventricular max dp/dt, regional left ventricular shortening and Lt ventricular work in treated groups compared to untreated groups[7].

ADVERSE DRUG REACTION[4].

Mild gastrointestinal complaints have been reported during long term administration of oral L-Carnitine. These include nausea and vomiting, abdominal cramps and diarrhea.

PRECAUTIONS[4]

* L-Carnitine is not mutagenic.
* No evidence of impaired fertility or harm to the fetus due to L-Carnitine.
* This drug should be used during pregnancy only if clearly needed.

* L-Carnitine is a normal component of human milk.

INTERACTIONS[4]

Drugs, such as Cephaloridine, Verapamil and Quinidine are found to inhibit renal re-absorption of L-Carnitine.

INDICATIONS[4]

1. Indicated in treatment of primary systemic carnitine deficiency, hereditary disorders affecting fatty acid metabolism.
2. In patients particularly those presenting with cardiomyopathy, skeletal myopathy, ischemic cardiomyopathy
3. In patients receiving long term haemodialysis
4. Reye-like syndrome
5. In preterm infants, acute neonatal crisis
6. Along with valproate therapy
7. In oligospermia.

PREPARATIONS AND DOSAGE[4]

The drug is available in Tablet form, injection form and oral solution form.

- Tablet contains 330 mg. of L-Carnitine
- Injection 5m1. contains lgm of L-Carnitine
- Oral solution each 10m1 contains lgm of L-Carnitine.

DOSAGE

Adults: Injection : lgm 2 times a day intravenously.

Tablet: 1 tablet 3 times a day.

Oral solution : 10-30 mg/Kg for a 50 Kg subject dosage should start at 1 gm/day (10ml/day) and can be increased depending on the therapeutic response.

Infants and Children: 50-100 mg/kg/day and can be increased slowly to a maximum of 3gm/day.

PATIENTS AND METHODS

The present study is to evaluate the efficacy and safety of Carnitine in CHF. Sixty patients were considered in this study who are admitted in cardiology department with diagnosis of Congestive Heart Failure at Government General Hospital, Guntur. The study comprised of two weeks for each patient. They were given 2gms of IV Carnitine per day for 1 week followed by lgm oral Carnitine tablets per day until follow up investigation along with other conventional drugs. Before and after 15 days of treatment echocardiogram was done, triglycerides were estimated. During hospital stay patients were monitored for symptom relief and side effects. Every day blood pressure, pulse rate and temperature were recorded. Results were tabulated and ‘t’ values 'p' values were calculated. Results shown graphically and in tabular form

RESULTS

It was observed that administration of Carnitine reduced congestive heart failure. It improved the ejection fraction. The mean ejection fraction value before treatment was 37.5% and after treatment was 54.08% which was statistically significant ($P<0.001$). It relieved fatigue, dyspnea more effectively and quickly. Orthopnea and Paroxysmal Nocturnal Dyspnea were relieved within 2 days; pulmonary rales disappeared within 2 to 4 days. Pedal edema reduced after 6 to 7 days. One patient had arrhythmia after treatment with Carnitine. He was excluded from this study and one patient complained of diarrhea, so Carnitine was temporarily stopped and continued later. He had no similar complaints on continuation of therapy. Two patients complained of palpitation and nausea for a while immediately after giving intravenous Carnitine during first two days of therapy. The symptoms were subsided on continuation of therapy. It was observed that Carnitine reduced Triglycerides levels in all patients. Mean Triglycerides levels before treatment was 223.11mg% and mean Triglycerides levels after treatment was 169.8 with a statistical significance $P<0.001$.

Table 1
Ejection Fraction Values in CHF patients before and after treatment with carnitine.

Before treatment	After treatment	P Value
37.5± 7.2	54.08 ± 10.49	<0.001

Table 2
Triglycerides values before and after treatment with carnitine

Before treatment	After treatment	P. Value
223.11±36.2	169.8±27.14	<0.001

DISCUSSION

The results in the present study suggested that Carnitine was an effective and well-tolerated drug in mild to moderate CHF. In all patients it decreases the CHF with beneficial improvement in cardiac function. 2gms of Carnitine/day had a significant effect on Ejection fraction of CHF patients. It was statistically very significant (P<0.001). As it increases the Ejection fraction, it improves the cardiac function and increases the coronary blood flow and decreases the ventricular dilation. It is also observed that Carnitine decreases dyspnea palpitation, orthopnea, PND and edema. During treatment no serious side effects were noted. The side effects of Carnitine were nausea, vomiting, diarrhoea and abdominal cramps. These effects usually resolve with a reduction in Carnitine dosage. All the patients were responded well to L-Carnitine. It reduced triglycerides levels (223.11 ± 36.2 to 169.8 ± 27.14) which was statistically significant (P<0.001). 2gms of Carnitineper day IV followed by lgm per day of oral Carnitine for 15 days significantly reduced the triglycerides levels. The exact mechanism of action of Carnitine is not very clear but, it is said to improve myocardial energy metabolism by increasing the use of free fatty acids and by reducing the coronary lactate outflow.

SUMMARY

Congestive heart failure is most important public health problem today.the two most common causes are coronary artery disease and HTN. There is evidence that atherosclerosis and deficient myocardial Carnitine are involved in the pathogenesis of CHF. Various inotropic drugs, diuretics and vasodilators used in treatment improved the CHF. Carnitine is very effective in CHF and it is statistically very significant (P<0.001). Carnitine also decreased the serum triglycerides levels which is statistically very significant (P<0.001).

CONCLUSION

Carnitine is very effective and safe in the treatment of mild to moderate CHF. The therapy should be started in early stages of CHF. Adverse effects are less when compared to other drugs. Because of high cost of this parenteral drug preparation, do not make us possible to do large number of patients. The use of Carnitine may be a novel option for the management of CHF. In view of its rapid pharmacodynamic actions associated with fewer incidences of adverse drug reactions this study required further evaluation.

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