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EFFECT OF L-CARNITINE SUPPLEMENTATION ON NT-PRO BNP LEVELS AND INTRADIALYTIC HYPOTENSION IN PATIENTS RECEIVING MAINTENANCE HEMODIALYSIS

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ABSTRACT

The objective of this study was to determine the effect of L-Carnitine supplementation on NT- Pro BNP levels and intradialytic hypotension in patients receiving maintenance hemodialysis. A randomized control trail was conducted in hemodialysis center Jinnah Post Graduate Medical Center Karachi in collaboration with University of Karachi. 60 subjects receiving maintenance hemodialysis were recruited in the study after applying inclusion and exclusion criteria and divided into two groups; Group A comprised 50 participants who were given L-Carnitine via oral route and group B comprised 10 participants who were administered L-carnitine via intra venous route. Oral L-carnitine supplementation in the form of L-Carnitine tablets 500 mg thrice daily was given under strict monitoring for 5 months. Intra venous L-Carnitine was given to group B as a dose of 20mg/kg IV bolus infused over 2-3 minutes, administered into intra venous line after every hemodialysis session (thrice a week) for 5 months. Intradialytic hypotension improved in both oral and intravenous groups (p value 0.000). NT-pro BNP levels were seen to decrease more significantly in the intravenous group (group B) as compared to the oral group (group A). L-carnitine supplementation for 5 months lead to an improvement in intradialytic hypotension and a reduction in NT-pro BNP levels. Hence L-carnitine has a good potential for the treatment of cardiac complications in hemodialysis patients.

Keywords: L-Carnitine, Hemodialysis, Intradialytic hypotension, NT-pro BNP, Supplementation, Deficiency.

INTRODUCTION

Levo Carnitine (L-Carnitine) is the transporter of long-chain fatty acids inside the mitochondria during beta oxidation. (Higuchi, 2018) The cardiac and skeletal muscles depend upon beta oxidation of fatty acids for energy requirements. L-carnitine is taken via the diet and synthesized endogenously by the kidney and liver (Sizova *et al*., 2019). End stage renal disease patients who are on maintenance hemodialysis develop L-carnitine deficiency. This is partly because of loss of carnitine during hemodialysis which leads to depletion of the body stores and secondly by dietary restrictions and anorexia and reduction of endogenous synthesis of carnitine by the kidneys (Takashima *et al*., 2021). Dietary carnitine is absorbed in the enterocytes and has a bioavailability of 54-87%. Dietary supplements of l-Carnitine (0.5-6 g) have bioavailability of 14-18% of the dose (Chewcharat *et al*., 2022).

Patients receiving maintenance hemodialysis often develop carnitine deficiency. Several clinical conditions are associated with the deficiency of carnitine in hemodialysis patients such as, muscular fatigue, myopathy, intradialytic muscle cramps, erythropoieitin resistant anemia and hypotension (Katalinic *et al*., 2018). Carnitine deficiency is also associated with disorders like dyslipidemia, cachexia, cardiac arrhythmia and glucose intolerance. Dialysis-associated carnitine deficiency leads to decreased free carnitine levels and elevation in the levels of acylcarnitine (Maruyama *et al*., 2018). The free carnitine levels is removed during hemodialysis, whereas acylcarnitine is accumulated which leads to an elevated plasma acylcarnitine to free carnitine. It is hypothesized that carnitine supplementation in hemodialysis patients having carnitine deficiency may lead to clinical benefits by improving several of the conditions associated with carnitine deficiency (Maruyama *et al*., 2018). Supplementation of carnitine has been found to have beneficial effects in cardiac patients. Carnitine concentration in plasma and tissues of hemodialysis patients is severely reduced due to its impaired synthesis and losses across the dialysis membrane (Nishioka *et al*., 2020). As hypocarnitinemia is associated with cardiovascular compications in these patients, therefore an improvement in cardiac function is associated with carnitine supplementation in these patients. However, conflicting results are obtained from previous studies. Cardiovascular disease are commonly seen in dialysis patients causing 40% mortality in this population (Sars *et al*., 2020). Intradialytic hypotension is defined as

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a systolic blood pressure of ≤ 100 mmHg or a drop in systolic blood pressure of greater than 10 mmHg, or a decrease in mean arterial pressure more than 30 mmHg associated with or without symptoms. The European Best Practice Guidelines (EBPG) have defined intradialytic hypotension as a decrease in blood pressure with or without symptoms requiring an intervention (Kanbay et al., 2020). The prevalence of intradialytic hypotension is 15–30% (Bazargani *et al*., 2022). Hypotension results because excessive ultrafiltration results in decreased cardiac output especially when the compensatory mechanisms like heart rate and vascular tone are inadequate. In order to treat IDH interventions during the dialysis session are given which include mannitol , midodrine, food intake, intradialytic exercise and intermittent pneumatic compression of the lower limbs (Hamedi-Kalajahi *et al*., 2022). However treatment protocol for prevention and management of intradialytic hypotension awaits further clinical investigation. N Terminal-pro BNP is a component of the natriuretic peptide category. This category regulates and modulates processes in the cardiovascular system. Brain natriuretic peptide (BNP) plays a main role in blood pressure regulation and maintenance of extracellular volume by stimulating natriuresis (Hamedi-Kalajahi *et al*., 2021). The myocardium of the ventricles produce BNP in response to increased stress of myocardial wall. Initially BNP is formed as a prehormone (proBNP). After its release in the blood circulation pro BNP is broken down into two parts , its biologically active form BNP which is its C-terminal fragment and the biologically inactive form which is the N-terminal fragment (NT-pro BNP). It has been proved that elevated NT-proBNP levels are associated with an increase in the risk of cardiovascular events. In cardiac patients, levels of both BNP and NT-proBNP are increased (Yano *et al*., 2021). Patients having stage 3-4 chronic kidney disease (CKD) have elevated NT-pro BNP levels, and in patients with stage 5 CKD receiving maintenance hemodialysis these levels are even more elevated. NT-proBNP levels are used as diagnostic and prognostic marker for detection of left ventricular disorders, congestive cardiac failure, coronary artery disease, myocardial infarction, renal failure, and tachyarrhythmias and are associated with residual diuresis and dialysis dose (Wang *et al*., 2021). NT-pro BNP being synthesized in the ventricle, is affected by increase in ventricular filling pressure and increased afterload. Researches have reported that supplementing hemodialysis patients with L-carnitine decreases oxidative stress and hence protects the cardiac muscles from free radicles and ischemic changes and hence results in improvement in left ventricular end diastolic dysfunction ((Morgans *et al*., 2021). The possible mechanism for this improvement in cardiac function is better endurance of ultrafiltration which leads to less episodes of intradialytic hypotension and other cardiac complications. Impaired energy metabolism together with increased myocardial energy consumption can lead to myocardial injury (Eser *et al*., 2022). This has lead to interventions aiming at improving the energy metabolism in the myocardium of hemodialysis patients. Fatty acid metabolism is the major source of energy generation in the mycocardium and hence disorders of fatty acid oxidation may lead to myocardial systolic and diastolic dysfunction (Morgans *et al*., 2021). Hence we designed a study to evaluate the effects of L-Carnitine supplementation in hemodialysis patients on cardiac function. Patients with End Stage Renal Disease are often excluded from clinical trials conducted on cardiac patients, despite the high prevalence of cardiovascular disease in these patients. Hence, a clinical goal is to identify the effect of intervention on serum biomarkers and different cardiovascular complication and stratification in hemodialysis patients. The aim of the present study was to evaluate the effect of Carnitine supplementation on NT-Pro BNP levels and intradialytic hypotension in patients receiving maintenance hemodialysis.

MATERIALS AND METHODS

A randomized control trial was carried out in hemodialysis unit of Jinnah Post Graduate Medical College, in collaboration with Department of Biochemistry of University of Karachi. A total of 60 subjects receiving maintenance hemodialysis were recruited in the study after applying inclusion and exclusion criteria and divided into two groups; Group A comprised 50 participants who were given L-Carnitine via oral route and group B comprised 10 participants who were administered L-carnitine via intra venous route. On the basis of systolic blood pressure the patients were further subdivided as group A1 and B1 diagnosed as having episodes of intradialytic hypotension (systolic BP ≤100mmHg) and Group A2 and B2 included subjects who had systolic blood pressure < 100mm Hg and received oral or intravenous carnitine supplementation respectively. Inclusion criteria was subjects above 18 years of age and receiving maintenance hemodialysis for over more than 6 months and receiving three dialysis sessions per week through low efficiency dialyzer. Exclusion criteria was subjects suffering from any other chronic illness like tuberculosis or malignancy, subjects who were diagnosed with a cardiac disease prior to initiation of hemodialysis.

Oral L-carnitine supplementation in the form of L-Carnitine tablets 500 mg thrice daily was given to 50 of the study participants under strict monitoring for 5 months. Intra venous L-Carnitine was given to 10 of the study subjects as initial dose of 10mg/kg IV bolus infused over 2-3 minutes, administered into intra venous line after hemodialysis session for one week with strict monitoring for any adverse effects, after one week the dose was

increased to 20mg/kg intra venous infusion (trade name Inj Metacartin by Allianz Pharma) after every dialysis session (thrice a week) for 5 months and later given a maintenance oral dose of 500mg Once daily for one month .The vitals were monitored daily during the course of supplementation. Complete general physical examination was done on every dialysis session. Any signs of distress were strictly monitored during the course of supplementation the drug. The supplementation was given after obtaining ethical approval and informed consent both written and verbal and under direct supervision of a Nephrologist. Blood samples were taken from arteriovenous shunt before initiation of carnitine supplementation and after completion of supplementation.The ethical approval was obtained from institutional review board of Jinnah Post Graduate Medical center Karachi (ref no. NO.F.2-81/2020-GENL/42532/JPMC).

Age, weight, height, BMI, systolic and diastolic blood pressure were recorded. To detect any improvement in cardiac function NT-pro BNP levels and systolic and diastolic blood pressure were recorded before and after intervention. Cut off for the diagnosis of intradialytic hypotension was systolic blood pressure ≤100mmHg.

NT-pro BNP levels were monitored using pro BNP/NTBNP Human ELISA kit.

IBM SPSS version 23 was used to analyze data. Paired T test was used for the comparison of values prior to and after L-Carnitine supplementation.

RESULTS AND DISCUSSION

This study was carried out to evaluate the effects of L-Carnitine supplementation on cardiac complications in hemodialysis patients. Significant results were obtained in this study. In our study the subjects of groups A and B ,receiving oral or intravenous supplementation respectively were divided into two groups A1 and B1 on the basis of intradialytic hypotension (cut off systolic blood pressure ≤100mm Hg (Kanbay et al., 2020)). In our study the episodes of intradialytic hypotension were seen to decrease significantly in both intravenous and oral treated groups, however BMI did not change significantly. These results are in accordance to some of the previous studies (Higuchi *et al*., 2016; Sugiyama., *et al* 2021) who have also shown that intradialytic hypotension improved significantly in levo carnitine treated group as compared to placebo. The findings of our study indicate that L-carnitine is a good option for the treatment of dialysis related cardiac complications. The deficiency of carnitine allters cellular metabolism and causes impairment in the energy production because of reduction in β-oxidation of fatty acids in the mitochondria resulting in accumulation of acylcarnitine which suppresses the metabolic action of several important enzymes. This impairment and altered metabolic state leads to dialysis related complications like dialysis related hypotension, muscle cramps, cardiovascular disorders and erythropoietin-resistant anemia (Mohammadi-Baneh *et al*., 2021). Previous studies conducted on hemodialysis patients have shown a beneficial effect of L-carnitine supplementation in improving left ventricular ejection fraction especially in patients with left ventricular hypertrophy (Maruyama *et al*., 2018; Nishioka *et al*., 2020). This improvement might help in decreasing intra dialytic hypotension episodes. The exact mechanism of this improvement is still unclear. In our study a significant decrease in NT-pro BNP levels was observed which was more significant in the intravenous treated group. Our study results correlate with the results of previous studies (Sugiyama *et al*., 2021; Chewcharat *et al*., 2022) which have also shown the beneficial effects of L-Carnitine supplementation in improving the cardiac function assessed by performing echocardiography and NT-pro BNP levels. Sugiyama et al showed that stopping carnitine after six months of supplementation led to an increase in NT-pro BNP levels again. Takashima et al. in their work have also reported a decline in NT-pro BNP levels in hemodialysis patients who were supplemented with L-carnitine. Hence we can conclude that L-Carnitine supplementation has a potential role in reducing NT-pro BNP levels in hemodialysis patients by decreasing cellular oxidative stress and increasing energy supply to the myocardium. If this supplementation is given early in the course of disease it will minimize the morbidity and mortality in hemodialysis patients occurring due to cardiovascular disorders.

This limitation of this study were that the sample size was small making the statistical power weak. Secondly, it was a short duration study which might have affected the efficacy of L-Carnitine in improvement of cardiac function. It was a randomized control trial however a double blind trial would have produced more reliable results. Therefore, we suggest that larger and longer duration clinical studies are required to further validate the effects of L Carnitine in the treatment of cardiac dysfunction in Hemodialysis patients.

Table 1. Anthropometric measurements of study participants.

Characteristics	**Mean ± SD**
Age (years)	**43.9±8.6**
Gender • **Males** • **Females**	 **29** **31**
Body Mass Index (kg/m2)	**25.7±5.1**
Weight (kg)	**69.9±9.3**
Height (m)	**166.0±11.4**

Table 2. Effect of Carnitine supplementation on systolic and diastolic blood pressures among different study groups.

PARAMETERS	**PRE INTERVENTION**	**POST INTERVENTION**	**P-VALUE**
ORAL GROUP A1 (IDH group) (n=14)			
SYSTOLIC BLOOD PRESSURE(mmHg)	92±7.7	103±5.5	**0.000**
DIASTOLIC BLOOD PRESSURE(mmHg)	52±10	62±7	**0.000**
ORAL GROUP A2 (n=36)			
SYSTOLIC BLOOD PRESSURE(mmHg)	128±13	125±13	**0.004**
DIASTOLIC BLOOD PRESSURE(mmHg)	69±10	72±7	**0.029**
IV GROUP B1 (IDH group) (n=4)			
SYSTOLIC BLOOD PRESSURE(mmHg)	93±5	111±2	**0.000**
DIASTOLIC BLOOD PRESSURE(mmHg)	53±15	63±8	**0.041**
IV GROUP B2 (n=6)			
SYSTOLIC BLOOD PRESSURE(mmHg)	138	130	0.215
DIASTOLIC BLOOD PRESSURE(mmHg)	75±5	75±5	-

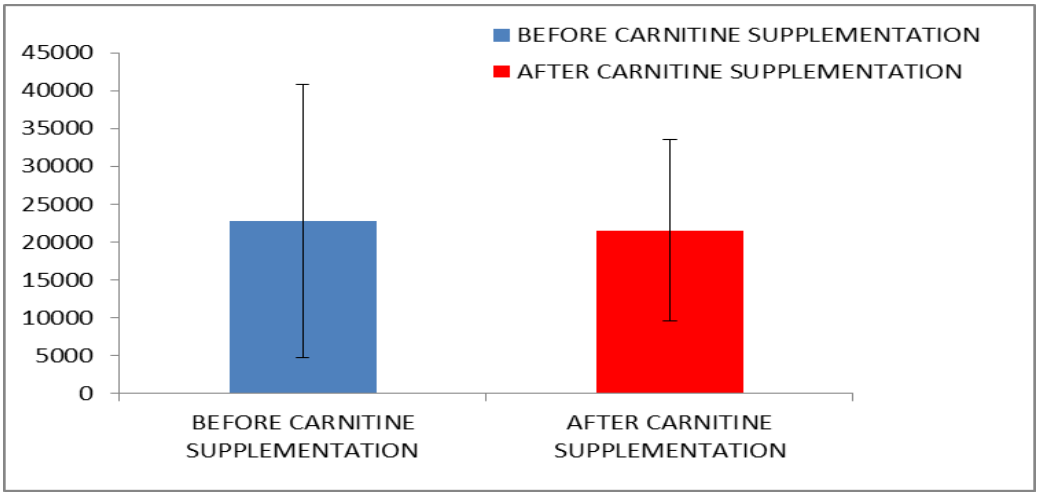

Fig. 1. Effect of oral L-carnitine supplementation on NT-pro BNP.
Oral group BNP Pre Post (n=50)

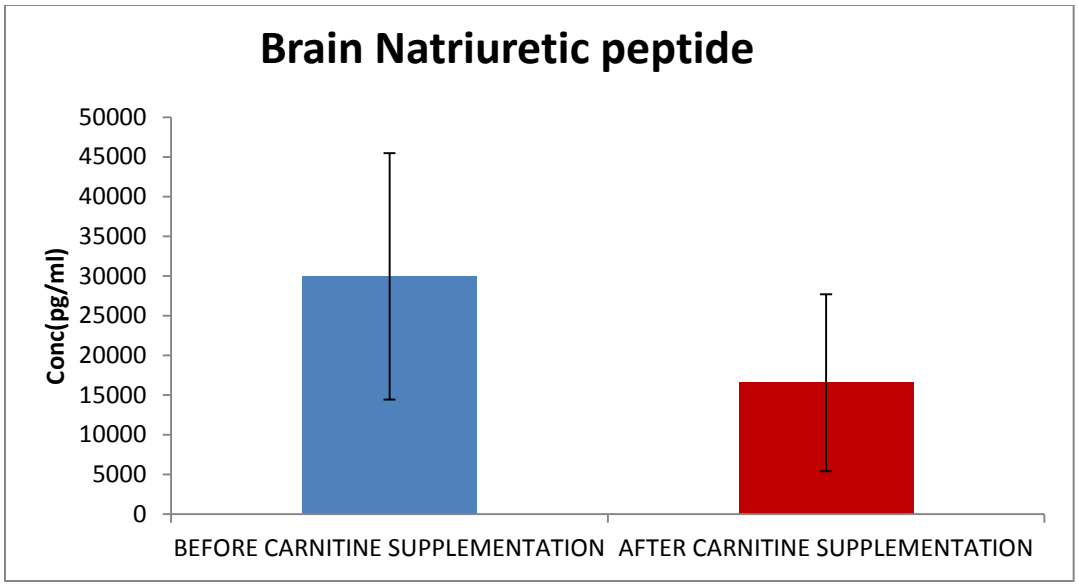

Fig.2. Effect of Intravenous L-carnitine supplementation on NT-pro BNP.
IV group BNP Pre Post (n=10)

CONCLUSION

L-carnitine supplementation for 5 months led to an improvement in intradialytic hypotension and a reduction in NT-pro BNP levels. Hence L-carnitine has a good potential for the treatment of cardiac complications in hemodialysis patients.

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