Effect of intravenous carnitine on hematological and renal parameters, erythropoietin dose, quality of life and Cardiac function in ESRD patients at PNS SHIFA hospital-A Quasi-expe...

Article · January 2013

CITATIONS
0

READS
91

3 authors, including:

Sohail Sabir

8 PUBLICATIONS **9** CITATIONS

SEE PROFILE

Aamir Ijaz

Rehman Medical Institute

89 PUBLICATIONS **120** CITATIONS

SEE PROFILE

ORIGINAL ARTICLE Pakistan Journal of Pathology 2013; 24(1): 12-17

Effect of intravenous carnitine on hematological and renal parameters, erythropoietin dose, quality of life and Cardiac function in ESRD patients at PNS SHIFA hospital- A Quasi- experimental study.

Sohail Sabir*, Aisha Bibi, Aamir Ijaz*****

* Department of Nephrology, Military Hospital, Rawalpindi, Pakistan.
**Department of Nephrology, PNS SHIFA, Karachi, Pakistan
***Head Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan.

ABSTRACT

Objectives: To evaluate the influence of carnitine therapy on skeletal myopathy, cardiomyopathy, heart failure, anemia and nutritional markers in an End Stage Renal Disease (ESRD) population.

Design, Setting and Participants: We conducted a prospective cohort study at Nephrology Department, PNS SHIFA, Karachi. A total of 35 patients were included. Blood sampling, two dimensional echocardiography imaging and quality of life (QOL) 36-item short form (SF36) survey was done at baseline, 3 months and at 6 months. At the end of 6 months data was collected and analyzed using SPSS 20.

Results: The age of the subjects was (mean $\pm$ SD) 46.55 ±16.64 with a male to female ratio of 2:1.There was statistically significant improvement at three and six months in QOL assessment SF36 questionnaire-based Physical Component Summary (PCS) and Mental Component Summary (MCS) ($p<0.001$ and 0.001), Haematocrit ($p<0.02$ and 0.004), pre and post dialysis serum urea ($p<0.051$ and 0.077) and ($p<0.037$ and 0.278) respectively, Transferrin saturation % ($p<0.654$ and 0.02), erythropoietin dose reduction per week ($p<0.08$ and 0.013), Ejection fraction improvement ($p<0.104$ and 0.023).

Conclusion: Intravenous L-carnitine in our ESRD patients lead to significant effects including improvement in hematological and renal parameters, improvement in cardiac function and quality of life and erythropoietin dose reduction.

Key Words: L-carnitine, Haemodialysis, ESRD, Anemia, quality of life, dialysis adequacy, crdiac function.

INTRODUCTION

Haemodialysis in patients with End Stage Renal Disease (ESRD) is not only aimed towards patient survival but also to improve their quality of life. Despite advances in dialysis therapy a large number of patients develop muscle weakness, easy fatigability and impaired daily living and professional capability. Kidney disease is accompanied by defective hormonal and biochemical homeostasis, which is dealt with appropriate correction using supplementary medicines. For this very reason, patients are regularly monitored and biochemical analysis done to reach target hemoglobin, dialysis adequacy, decreased myopathy, anemia etc. An important endogenous compound, carnitine, becomes deficient in ESRD patients on dialysis, termed as Dialysis- related Carnitine Disorder

Correspondence Address: Col Sohail Sabir, Head of the Nephrology Department and Classified Medical Specialist, Military Hospital, Rawalpindi.
Email: *drsohailsa@hotmail.com*

(DCD).This disorder encompasses anemia which is hypo responsive to erythropoietin treatment; cardiomyopathy, skeletal muscle dysfunction, and dialysis adequacy [1].

Carnitine is an endogenous compound required for transfer of long chain fatty acids into the inner matrix of mitochondria, thereby delivering these substances for beta oxidation and energy production [2]. In healthy individuals carnitine is derived from diet and synthesized from amino acids in liver and kidney. Body pool of carnitine is maintained within narrow limits. A large portion of carnitine is stored in skeletal muscle and myocardial

muscle [3,4]. A healthy kidney is an important part in conserving this homeostasis by significant reabsorption of the filtered carnitine. In patients with ESRD not on dialysis, the carnitine levels are high since dietary intake and synthesis doesn't match with the impaired absorption of carnitine from the diseased kidney [5,6]. While in ESRD patients on dialysis this is reversed, the levels of plasma become low (including skeletal muscle and cardiac muscle) [7,8]. This deficiency is related mainly to the duration of haemodialysis, as per KDOQI clinical practice guidelines for cardiovascular diseases in dialysis patients 2005: heamodialysis therapy for more than 6 months is associated with reduction of plasma and tissue levels of carnitine and carnitine esters [5].

Evans *et al (2000)* found that almost 75%of levocarnitine is removed from plasma during each haemodialysis session, resulting in a progressive decline in L-carnitine [4]. Another study concluded that as many as 95% patients on maintenance haemodialysis suffer DCD and are prone to increased hospitalization [9]. A number of studies have been conducted to investigate the important role of carnitine and its increased clearance due to dialysis [2-,4]. Many studies have assessed the efficacy of L- carnitine treatment in dilated cardiomyopathy [10-14]. One study showed an increase in ejection fraction ($p<0.05$ according to variance analysis). In this study EF before the treatment was 44.99 % and at the end of the study i.e. 60^{th} day was 51.48% [11]. Apart from that, role of L-carnitine in supplementation EPO dose /hematocrit levels in dialysis patients has been investigated in many studies. These studies in general, investigated the effects of L-carnitine treatment on renal anemia, and led to the conclusion that carnitine supplementation had significantly improved the response to erythropoietin treatment [15,16]. Duranay *et al (2006)* assessed the effects of L-carnitine in on inflammatory and nutritional markers in haemodialysis patients and found that L-carnitine treatment has significant benefits on CRP, total protein, albumin and transferring saturation [17].

Our study aimed at assessing the influence of L-carnitine therapy on dialysis adequacy, nutritional markers and transferrin saturation in ESRD patients on dialysis.

MATERIAL & METHODS

Study Design: We conducted a quasi-experimenal study at Nephrology Department PNS SHIFA, Karachi (a tertiary care hospital).This study was conducted with the approval of Ethics Review Committee. A total of 40 patients were inducted, who all had been undergoing haemodialysis at the same department at least for the last 6 months. The patients were explained the purpose and applications of the study, following which oral and written permission was obtained.

Inclusion criteria: Patients on maintenance haemodialysis three times a week for at least six months and had not received any L-carnitine treatment previously.

Exclusion criteria: Patients who did not consent to enter the study; who received L-carnitine containing products in last six months (either orally or intravenous).

Data collection and analysis: The study variables included measurement of haemodialysis adequacy indicator (Kt/V), hemoglobin, erythropoietin dose, albumin, phosphate, ejection fraction and quality of life (QOL) assessment by SF36 questionnaire. The observed parameters were both objective laboratory data and subjective assessment. The tests were done at the baseline, at three months and six months after L-carnitine treatment. The patients were dialyzed for 4 hours three times each week using Polysulphane hollow fibers membranes and bicarbonate dialysate. L-carnitine (KEFEI) 20mg/kg was used intravenously after each dialysis session.

To evaluate the efficacy of L-carnitine treatment in heart failure symptoms/ cardiomyopathy, two dimensional M mode and continuous Doppler echocardiography were done with standard technique. The echocardiograph used was sonolayer-SSH-60 Toshiba model. Ejection fraction was calculated at baseline, three months and at six

months. Measurement of the patients' functionality/ QOL was done by a previously validated self-report instrument i.e. Medical outcomes study 36-item short form (SF36).

Biochemical analysis: Blood samples for hemoglobin (Hb), albumin, haematocrit (Hct), Total Red Blood Cells Count (TRBC), phosphate and percentage transferrin saturation (TSAT) were obtained before the dialysis session at baseline, at three months and at the end of six months. Hb, Hct, TRBC were analyzed on Sysmex21 while albumin, iron, TIBC, urea and creatinine were analysed on in a Roche Modular P-800® analyzer with original reagent. TSAT was calculated by using serum iron and TIBC.

Study endpoints: The study aimed at demonstrating the effect of carnitine supplementation on dialysis adequacy, nutritional markers and TSAT in ESRD patients on dialysis.

RESULTS

Our study included 40 patients as per inclusion criteria but 2 patients did not give consent and declined to be enrolled. One patient developed severe chest pain after second injection and opted out of the study. One patient developed repeated shivering after getting injection carnitine on first two successive doses and opted out of the study. One patient shifted over to another dialysis centre after three injections and so opted out of the study. The remaining 35 patients completed the study period. The mean age of our study patients was (mean$\pm$SD) 46.55 ±16.64 with a male to female ratio of 2:1, mean hemodialysis duration in months was 43.35±12.15 and mean Kt/V was 1.14±0.29 (Table-1). The different study parameters which showed statistically significant improvement at three and six months are depicted in Table-2. There was statistically significant improvement both at three and six months in quality of life evaluation through SF 36 Physical Component Summary (PCS) ($p< 0.001$ and $p< 0.001$) and SF 36 Mental Component Summary (MCS) ($p<0.001$ and $P< 0.001$). Haematocrit improvement was statistically significant both at three months and six months ($p<0.02$ and 0.004). There was statistically significant decrease both at three and six months in pre dialysis serum urea ($p<0.051$ and 0.077) and post dialysis serum urea ($p<0.037$ and 0.278). TSAT improved at three months but was only statistically significant at six months ($p<0.654$ and 0.02). There was statistically significant reduction in erythropoietin dose per week both at three and six months ($p<0.08$ ad 0.013). There was statistically significant improvement in Ejection fraction on 2D echo both at three and six months ($p<0.104$ and 0.023). Although there was improvement in other parameters which were studied including serum albumin, serum phosphate levels, blood glucose, Ultrafiltration, weight and intra-dialytic hypotension, these were statistically non-significant.

DISCUSSION

In our study we did not measure carnitine serum levels as it has been previously endorsed by American Association of Kidney Disease Consensus Group that serum levels are not a good predictors of clinically effective carnitine dose [18]. Our data shows that there was improvement in haematocrit and TSAT which is in agreement with studies by Matsumoto *et al* (2000) and Nikolaos *et al* (2000) [19,20]. However, Caruso *et al* (1998) found no benefit [21]. The erythropoietin dose reduction found at end of our study is in agreement with other studies done by Labonia *et al* (1995) and Kletzmayr *et al* (1999) [22.23]. In these studies it was highlighted that this effect is significantly pronounced with intravenous L-carnitine. Cardiovascular mortality is significant among ESRD patients and studies have shown improvement in systolic and diastolic function [24-26]. Our study also showed statistically significant improvement in ejection fraction. A meta-analysis by Savica *et al* (1999) showed that thirty seven percent of study patients had statistically significant improvement in left ventricular ejection fraction [27]. It also showed reduction in muscle weakness, frequency of muscle cramps and intradialytic hypotension. However, in our study population muscle cramps and intradialytic hypotension were insignificant symptoms at the baseline. This meta-analysis also showed improvement in quality of life and dialysis adequacy which has been substantiated by

our findings of statistically significant improvement in scores of SF 36 PCS/MCS as well as the improvement in pre and post dialysis serum urea. The change in Kt/v was not significant, however, because of the reason that the baseline dialysis adequacy was already within the standard parameters in our study patients.

Table 1: Demographic data for thirty five patients included in the study

Parameter	**n=35**
Male/female ratio	2:1
Mean HD duration (months)	43.35±12.15
Mean Age (years)	46.55±16.64
Original kidney disease Unknown Diabetes Mellitus Hypertension Chronic glomerulonephritis Obstructive uropathy Lupus Nephritis	 7 9 8 6 4 1
Mean Kt/V	1.14 ± 0.29

Table 2: Study parameters at baseline, at three months and at six months

Baseline Parameters	**Three months (p-value)**	**Six months (p-value)**
Haematocrit 31.45±.034	33.60±.039 Increased (0.02)	35.00±.036 Increased (0.004)
Mean Erythropoietin dose per week 17333.33±2743	15555.56±3184 Decreased (0.08)	12875.00±2629 Decreased (0.013)
Mean SF 36 PCS score 35.94±12.11	45.74±12.10 Improved (0.001)	49.79±10.55 Improved (0.001)
Mean SF 36 MCS score 43.73±12.781	52.88±8.607 Improved (0.001)	56.88±5.65 Improved (0.001)
Mean Transferrin saturation % 17.74±1.20	17.99±0.94 Increased (0.654)	20.138±1.89 Increased (0.020)
Mean Ejection Fraction% (2 D echo) 50±13.72	52.81±12.37 Increased (0.104)	54.81±10.85 Increased (0.023)
Mean Pre-dialysis Serum urea 23.138±8.9178	19.625±4.78 Decreased (0.051)	19.900±5.57 Decreased (0.077)
Mean Post-dialysis Serum Urea 8.44±2.90	7.013±2.90 Decreased (0.037)	7.71±2.69 Decreased (0.278)

CONCLUSION

Intravenous L-carnitine in our ESRD patients lead to significant effects including improvement in hematological and renal parameters, improvement in cardiac function and quality of life and erythropoietin dose reduction which are in tandem with the previous similar studies on the subject.

REFERENCES

1. Evans AM. Dialysis-Related carnitine disorder and levocarnitine pharmacology. Am J Kidney Dis 2003; 41(4): 13-26.
2. Evans AM, Faull RJ, Nation RL, Prasad S, Elias T, Reuter SE, *et al*. Impact of hemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. Kid Int 2004; 66:1527-34.
3. Evans AM, Faull RJ, Fornasini G, Lemanowicz EF, Longo A, Pace S, *et al*. Pharmacokinetics of L-carnitine in patients with end-stage renal disease undergoing long-term hemodialysis. Clin Pharmacol Ther 2000; 68: 238-49.
4. Fornasini G, Richard NU, Evans AM. A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. Br J Clin Pharmacol 2007; 64(3): 335-45.
5. Eknoyan G, Latos DL, Lindberg J. Practice recommendation for the use of L-carnitine in dialysis-related carnitine disorder. National Kidney Foundation Carnitine Consensus Conference. Am J Kid Dis 2003; 41(4): 868-86.
6. Schreiber B, Lewis V. Management of carnitine deficiency in ESRD patients undergoing dialysis: challenges and considerations. Dial Transplantat. 2001; 30(4): 207–212.
7. Schreiber B. Levocarnitine therapy is rational and justified in selected dialysis patients. Blood Purif 2006; 24: 128-39.
8. Weinhandl ED, Rao M, Gilbertson DT, Collins AJ, Pereira BJG. Protective effect of intravenous levocarnitine on subsequent-month hospitalization among prevelant hemodialysis patients, 1998 to 2003. Am J Kid Dis 2007; 50(5): 803-12.
9. Kazmi WH, Obrador GT, Sternberg M, Lindberg J, Schreiber B, Lewis V, *et al*. Carnitine therapy is associated with decreased hospital utilization among hemodialysis patients. Am J Nephrol 2005; 25: 106-115.
10. Pauly DF, Pepine CJ. The role of carnitine in myocardial dysfunction. Am J Kid Dis. 2003; 41(4): 35-43.
11. Dönder E, Çolak R, Karaoğlu A, Ayhan O, Özkan Y. The efficacy of L-Carnitine treatment in dilated cardiomyopathy. Tr J Med Sc 1998; 28 :619-23.
12. Reddy V, Bhandari S, Seymour AML. Myocardial function, energy provision and carnitine deficiency in experimental uremia. J Am Soc Nephrol 2007; 18: 84-92.
13. Lango R, Smolenski RT, Narkiewicz M, Suchorzewska J, Lysiak-Szydlowska W. Influence of L-carnitine and its derivatives on myocardial metabolism and function in ischemic heart disease and during cardiopulmonary bypass. Cardiovascular Research 2001; 51: 21-29.
14. Miller B, Ahmad S. a review of the impact of L- carnitine therapy on patient functionality in maintenance hemodialysis. Am J Kid DIs. 2003; 41(4): 44-48.
15. Reuter SE, Fault RJ, Ranieri E, Evans AM. Endogenous plasma carnitine pool composition and response to erythropoietin treatment in chronic haemodialysis patients. Nephrol Dia Transplant 2009; 24: 990-996.
16. Calò LA, Davis PA, Pagnin E, Bertipaglia L, Naso A, Piccoli A, *et al*. Carnitine-medicated improved response to erythropoietin involves induction of haem oxygenase-1: studies in humans and in an animal model. Nephrol Dia Transplant 2008; 23: 890- 95.
17. Duranay M, Akay H, Yilmaz FM, Senes M, Tekeli N, Yücel D. Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. Nephrol Dia Transplant 2006; 21:3211-3214.

18. Consensus Group Statement: Role of L-carnitine in treating renal dialysis patients. Dial Transplant. 1994; 23:177-81.
19. Matsumoto Y, Sato M, Ohashi H, Araki H, Tadokoro M, Osumi Y, *et al*. Effects of L-carnitine supplementation on cardiac morbidity in hemodialyzed patients. Am J Nephrol 2000; 20 (3): 201-207.
20. Nikolaos S, George A, Telemachos T, Maria S, Yannis M, Konstantinos M. Effect of L-carnitine supplementation on red blood cell deformability in hemodialysis patients. Ren Fail 2000; 22: 73-80.
21. Caruso U, Leone L, Cravotto E, Nava D. Effects of L-carnitine on anemia in aged hemodialysis patients treated with recombinant human erythropoietin: A pilot study. Dial Transplant 1998; 27:498–506.
22. Labonia WD. L-carnitine effects on anemia in hemodialyzed patients treated with erythropoietin. Am J Kidney Dis 1995; 26:757-64.
23. Kletzmayr J[1], Mayer G, Legenstein E, Heinz-Peer G, Leitha T, Hörl WH, *et al*. Anemia and carnitine supplementation in hemodialyzed patients. Kidney Int 1999; 69:93-106.
24. Sakurabayashi T, Takaesu Y, Haginoshita S, Takeda T, Aoike I, Miyazaki S, *et al*. Improvement of myocardial fatty acid metabolism through L-carnitine administration to chronic hemodialysis patients. Am J Nephrol 1999; 19: 480-84.
25. Pauly DF, Pepine CJ. The role of carnitine in myocardial dysfunction. Am J Kidney Dis 2003; 41(4): 35-43.
26. Romagnoli GF, Naso A, Carraro G, Lidestri V. Beneficial effects of L-carnitine in dialysis patients with impaired left ventricular function: An observational study. Curr Med Res Opin 2002; 18: 172-175.
27. Savica V *et al*. Dialysis- induced carnitine deficiency. A meta-analysis evaluation of clinical results. J Amer Soc Nephrol 1999; 13: 302-306