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EFFECT OF LEVOCARNITINE INJECTIONS ON REDUCING ERYTHROPOIETIN-STIMULATING AGENT REQUIREMENTS IN HEMODIALYSIS PATIENTS WITH RENAL ANEMIA

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Name of Author:
Shazia Abbas[1]*, Mateen Akram[2], Sibgha Ahmed[3], Sameer Sattar[4], Palwisha Ameen[5], Muhammad Usman Masood Butt[6]

Affiliation: *[1]Nephrology Trainee, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, shaziafsheikh16@gmail.com*
[2]Associate professor, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, drmateen73@hotmail.com
[3]Trainee Registrar, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, sibghaahmed97@gmail.com
[4]Trainee Registrar, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, sameersattar32@gmail.com
[5]Post graduate resident, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, palwasha_ameen@hotmail.com
[6]Doctor, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, Usmanmasood.94@gmail.com

Corresponding Author:
Dr. Shazia Abbas
shaziafsheikh16@gmail.com

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Abstract: Background: Anemia is frequent in maintenance hemodialysis (MHD) patients and requires high erythropoietin (EPO) doses. Intravenous (IV) levocarnitine may reduce EPO need.**Objective:** To assess changes in hemoglobin (Hb), hematocrit (Hct), weekly EPO dose, and erythropoietin resistance index (ERI) after adjunctive IV levocarnitine in MHD patients over six months.
Methods: This prospective observational cohort was conducted at Shaikh Zayed Hospital, Lahore. Ninety-four MHD patients were enrolled from 10 April 2025 to 10 October 2025. Forty-seven received IV levocarnitine 1,000 mg after dialysis, thrice weekly, with EPO therapy. Forty-seven controls received EPO alone. EPO was prescribed weekly and titrated by protocol using Hb, Hct, and ERI. Outcomes were recorded monthly.**Results:** Baseline Hb did not differ between groups, with values of 8.79 ± 0.31 g/dL in the levocarnitine group and 8.87 ± 0.32 g/dL in controls; p=0.1849. Monthly follow-up showed significantly higher Hb and Hct from Month 2 onward and significantly lower weekly EPO dose and ERI from Month 3 onward in the levocarnitine group compared with controls (p<0.01). At Month 6, Hb, Hct, weekly EPO dose, and ERI were 12.00 ± 0.38 g/dL, 36.19 ± 1.23%, 7714.89 ± 1053.66 units/week, and 10.07 ± 2.00 in the levocarnitine group; control values were 9.77 ± 0.33 g/dL, 29.29 ± 1.32%, 11093.62 ± 1366.11 units/week, and 17.36 ± 2.46. **Conclusion:** Adjunctive IV levocarnitine was associated with better anemia indices and lower EPO requirement. It may be useful as an EPO dose-sparing adjunct where EPO cost is a concern.

Keywords: Anemia, Erythropoietin, Erythropoietin resistance index, Hemodialysis, Levocarnitine.

INTRODUCTION

Anemia is common in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis (MHD). It causes fatigue, poor exercise tolerance, reduced quality of life, and greater dependence on erythropoietin (EPO) therapy. A Pakistani study on ESRD patients receiving MHD reported anemia in a large proportion of patients.[1] A multicenter Pakistani study also showed that anemia was highly prevalent among dialysis patients and was associated with treatment burden and poor health-related quality of life (HRQoL).[2]

EPO remains an important part of anemia management in MHD patients. However, some patients need higher EPO doses to achieve or maintain an acceptable hemoglobin (Hb) level. This poor response is commonly assessed by the erythropoietin resistance index (ERI), which relates EPO dose to body weight and Hb response. A large MHD cohort showed that ERI is affected by clinical factors and is associated with patient outcomes.[3] Iron imbalance and parathyroid hormone (PTH) levels have also been linked with ERI in MHD patients.[4] Oxidative stress may further contribute to EPO resistance by affecting erythrocyte survival and hematological response.[5]

Levocarnitine is a dialyzable compound involved in mitochondrial fatty acid transport and cellular energy metabolism. Long-term MHD may reduce carnitine availability because of dialysis-related loss, reduced intake, and impaired endogenous synthesis. This provides a biological rationale for using intravenous (IV) levocarnitine as an adjunctive treatment in selected MHD patients with anemia. A Pakistani randomized controlled trial reported that IV levocarnitine improved Hb and iron profile more effectively than oral levocarnitine in MHD patients.[6] In contrast, a regional clinical trial from Iran found no significant post-treatment difference in Hb between EPO alone and EPO plus L-carnitine.[7] Another clinical study reported that levocarnitine combined with iron sucrose improved anemia-related outcomes in uremic patients with renal anemia.[8]

Available evidence on levocarnitine supplementation in maintenance hemodialysis patients remains inconsistent. Previous studies have reported variable effects on hemoglobin, hematocrit, erythropoietin dose, and ERI. Some studies have suggested that levocarnitine may reduce erythropoietin requirement and improve erythropoietin responsiveness, particularly when given for an adequate duration and through the intravenous route.[6–9] However, differences in study design, route of administration, dose, treatment duration, baseline carnitine status, iron management, dialysis adequacy, and patient selection have limited firm conclusions. Therefore, further prospective data are needed to clarify whether intravenous levocarnitine can serve as an erythropoietin dose-sparing adjunct in routine hemodialysis practice.

In Pakistan, the burden of chronic kidney disease and end-stage renal disease is increasing, while access to long-term dialysis and erythropoietin therapy remains financially challenging for many patients and healthcare systems.[7] In such resource-constrained settings, adjunctive strategies that reduce erythropoietin requirement without compromising anemia control may have important clinical and economic value. However, local prospective evidence evaluating intravenous levocarnitine as an erythropoietin dose-sparing adjunct in maintenance hemodialysis patients remains limited. Therefore, this study aimed to assess changes in anemia indices and erythropoietin requirements following adjunctive intravenous levocarnitine in maintenance hemodialysis patients over a six-month period.

METHODS

This prospective cohort study was conducted in the Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan, from 10 April 2025 to 10 October 2025. The sample size was calculated using the World Health Organization sample size calculator for comparison of two independent means. Based on the expected difference in weekly erythropoietin dose from previously published data, with a two-sided 5% significance level, 80% power, and 1:1 allocation, the required sample size was 47 participants per group. Therefore, a total of 94 patients were included in the study.[9] Non-probability consecutive sampling

technique was used for sample selection.

Adults aged 18–80 years receiving thrice-weekly maintenance hemodialysis for at least three months were enrolled after written informed consent. Patients were required to be clinically stable for at least 4 weeks, with no changes to their dialysis prescription beyond routine adjustments. Eligible patients were receiving anemia management with erythropoietin, with either a stable erythropoietin dose for at least four weeks or a documented erythropoietin resistance index from the preceding month. Moreover, screening hemoglobin within the program target range of approximately 8.0–11.5 g/dL, iron-replete status or correction of iron deficiency according to local criteria, adequate dialysis such as spKt/V ≥1.2, ability to provide informed consent, and ability to complete six months of monthly follow-up.

Exclusion criteria included active intercurrent illness, including sepsis, pneumonia, urinary tract infection, vascular access infection, acute coronary syndrome, stroke, or any acute condition requiring hospital admission or systemic antibiotic therapy within the preceding four weeks; active infection defined as fever ≥38°C or ongoing systemic antibiotic therapy; recent transfusion, major surgery, or overt bleeding within the preceding three months; uncorrected iron, folate, or vitamin B12 deficiency according to local laboratory criteria; haematological disorders, including haemoglobinopathies, bone marrow failure, or active malignancy receiving cytotoxic or marrow-suppressive therapy; uncontrolled secondary hyperparathyroidism requiring urgent intervention; severe hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal or clinically documented decompensated liver disease; decompensated heart failure defined as New York Heart Association class III–IV symptoms or hospital admission for heart failure within the preceding three months; uncontrolled hypertension (repeated pre-dialysis blood pressure ≥180/110 mmHg despite antihypertensive treatment); clinically significant arrhythmia (arrhythmia requiring active anti-arrhythmic treatment, emergency care, or hospital admission within the preceding three months) pregnancy or lactation; hypersensitivity to levocarnitine; therapeutic carnitine use within the previous three months; planned renal transplant, change of dialysis modality, relocation, or participation in another interventional study; contraindication to erythropoietin therapy under local policy; and any condition likely to compromise protocol adherence, safety monitoring, or outcome validity.

After eligibility assessment, patients were grouped according to the treatment decision made by the treating nephrologist. Patients who were prescribed adjunctive intravenous levocarnitine by the treating nephrologist were included in the levocarnitine group, whereas eligible patients who continued erythropoietin therapy without levocarnitine were included in the control group.

Baseline demographic characteristics, comorbidities, dialysis-related details, dry weight, hemoglobin, and hematocrit were recorded at enrolment. Participants were then followed monthly for six months. At each monthly follow-up, hemoglobin, hematocrit, weekly erythropoietin dose, adverse events, and erythropoietin resistance index were recorded on a structured proforma. Erythropoietin resistance index was used as an indirect functional measure of erythropoietin resistance and was calculated as weekly erythropoietin dose in units/week divided by dry weight in kilograms multiplied by average hemoglobin in g/dL.

Both groups received recombinant human erythropoietin according to a standardized titration algorithm guided by hemoglobin, hematocrit, and erythropoietin resistance index. Initial erythropoietin dosing followed prespecified ranges, with higher doses for hemoglobin <10 g/dL or hematocrit <30%, and dose tapering for maintenance when hemoglobin was 11–12 g/dL or hematocrit was 33–36%. Erythropoietin dose was reduced by 25% if hemoglobin increased by >1 g/dL within two months, maintained when hemoglobin remained between 10 and 12 g/dL, and increased by 25% if hemoglobin persisted <10 g/dL or hematocrit remained <30% after two months. The primary endpoints were weekly erythropoietin requirement and erythropoietin resistance index. Monthly hemoglobin, hematocrit, erythropoietin dose, erythropoietin resistance index, adverse events, and dialysis-related details were recorded from Month 1 to Month 6.

Ethical Approval

Ethical approval for this study was granted by the Technical & Ethical Review Committee (TERC), Institutional Review & Research Advisory Board (IRRAB), Shaikh Zayed Medical Complex, Lahore (TERC ID: TERC/SC/INT/2025/455) on 14-03-2025.

Statistical Analysis

Data were analyzed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequency and percentage. An independent-samples t-test was used to compare baseline continuous variables between the LVC and CTL groups. These variables included age, height, weight, body mass index, Haemoglobin, and hematocrit. The chi-square test was used to compare categorical variables (hypertension and diabetes

mellitus) between groups. For month-wise comparisons of Haemoglobin, hematocrit, erythropoietin dose, and erythropoietin resistance index (ERI), an independent-samples t-test was used at each time point. This test was applied to compare the LVC and CTL groups separately at each month. To check the difference between the Levocarnitine (LVC) and Control (CTL) groups, a Two-Way Repeated Measures ANOVA was performed.

To account for baseline imbalance and repeated observations within the same patient, linear mixed-effects models were used as the primary longitudinal analysis for Hb, Hct, weekly EPO dose, and ERI. Patient identity was entered as a random intercept, while group, month, and group × month interaction were entered as fixed effects. The models were adjusted for age, weight, DM status, and the baseline value of the relevant outcome. Baseline Hb was used for the Hb, EPO dose, and ERI models, whereas baseline Hct was used for the Hct model. Month-wise independent-samples t-tests were used only as supplementary time-point comparisons. Because repeated monthly comparisons may increase the risk of type I error, their p-values were evaluated using Holm correction within each outcome across the six-month follow-up. A p-value <0.05 was considered statistically significant.

RESULTS

There were 94 patients in the study. The overall mean age was 53.31 ± 9.42 years. There were 54 males and 40 females. The mean body mass index was 24.66 ± 3.76 kg/m². Hypertension was present in 73 patients, and diabetes mellitus in 44. The mean baseline hemoglobin and hematocrit were 8.83 ± 0.32 g/dL and 26.38 ± 1.51%, respectively (Table 1).

Table 1. Overall baseline characteristics of the study participants

Variable	Overall study population (n=94)
Age (years)	53.31 ± 9.42
Male sex	54 (57.4%)
Female sex	40 (42.6%)
Height (cm)	162.20 ± 7.78
Weight (kg)	64.43 ± 7.69
Body mass index (kg/m²)	24.66 ± 3.76
Hypertension	73 (77.7%)
Diabetes mellitus	44 (46.8%)
Baseline hemoglobin (g/dL)	8.83 ± 0.32
Baseline haematocrit (%)	26.38 ± 1.51

Table 2 shows the month-wise comparison of Hb, Hct, erythropoietin dose, and ERI between the two groups. An independent-samples t-test was used at each time point to compare the Levocarnitine and Control groups separately for each outcome. At Month 1, Hemoglobin was slightly higher in the control group, whereas hematocrit and erythropoietin dose did not differ significantly. ERI was significantly higher in the levocarnitine group at Month 1. From Month 2 onward, Hemoglobin and hematocrit became significantly higher in the levocarnitine group. From Month 3 onward, erythropoietin dose and ERI became significantly lower in the levocarnitine group. By Month 6, all outcomes showed significant improvement in favor of the levocarnitine group.

Table 2. Monthly outcomes in both groups

Time	Study Group (Levocarnitine)	Control Group	Unadjusted p-value	Holm-adjusted p-value
Hemoglobin (g/dL)				
Month 1	8.78±0.27	8.90±0.30	0.04*	0.04*
Month 2	9.44±0.25	9.05±0.27	<0.01*	<0.01*
Month 3	10.02±0.29	9.23±0.30	<0.01*	<0.01*
Month 4	10.75±0.32	9.42±0.29	<0.01*	<0.01*
Month 5	11.36±0.30	9.58±0.33	<0.01*	<0.01*
Month 6	12.00±0.38	9.77±0.33	<0.01*	<0.01*
Hematocrit (%)				
Month 1	26.14 ± 1.24	26.66±1.42	0.06*	0.06*
Month 2	28.41 ± 1.40	27.29±1.32	<0.01*	<0.01*
Month 3	30.06 ± 1.32	27.93±1.40	<0.01*	<0.01*

Month 4	32.24 ± 1.26	28.57±1.43	<0.01*	<0.01*
Month 5	34.14 ± 1.39	28.92±1.49	<0.01*	<0.01*
Month 6	36.19 ± 1.23	29.29±1.32	<0.01*	<0.01*
Erythropoietin dose (units/week)				
Month 1	12174.47 ±1170.42	11968.09 ±1297.88	0.42	0.42
Month 2	11287.23 ±1171.00	11804.26 ±1349.51	0.05*	0.10
Month 3	10410.64 ±1079.40	11621.28 ±1338.87	<0.01*	<0.01*
Month 4	9445.74 ±980.29	11468.09 ±1366.34	<0.01*	<0.01*
Month 5	8659.57 ±1006.70	11244.68 ±1463.85	<0.01*	<0.01*
Month 6	7714.89 ±1053.66	11093.62 ±1366.11	<0.01*	<0.01*
Erythropoietin resistance index				
Month 1	22.46 ± 3.98	20.57±2.78	0.01*	0.02*
Month 2	19.34 ± 3.53	19.92±2.69	0.37	0.37
Month 3	16.82 ± 3.08	19.27±2.73	<0.01*	<0.01*
Month 4	14.25 ± 2.65	18.63±2.70	<0.01*	<0.01*
Month 5	12.35 ± 2.33	17.93±2.63	<0.01*	<0.01*
Month 6	10.07 ± 2.00	17.36±2.46	<0.01*	<0.01*

Linear mixed-effects regression was performed to adjust for baseline imbalance and repeated observations within the same patient. After adjustment for age, weight, diabetes mellitus status, and baseline values, the group × month interaction remained significant for hemoglobin, hematocrit, weekly erythropoietin dose, and erythropoietin resistance index. These findings show that patients receiving adjunctive intravenous levocarnitine had a greater improvement in anemia indices and a greater reduction in erythropoietin requirement over time compared with the control group (see Table 3).

Table 3: Adjusted linear mixed-effects regression analysis for monthly anemia-related outcomes in the levocarnitine and control groups

Outcome	Predictor	Adjusted β	p-value
Hemoglobin	Group	-0.061	0.231
Hemoglobin	Month	0.174	<0.001*
Hemoglobin	Group× Month	0.472	<0.001*
Hemoglobin	Age	-0.001	0.791
Hemoglobin	Weight	0.002	0.511
Hemoglobin	DM	0.001	0.976
Hemoglobin	Baseline value	0.532	<0.001*
Hematocrit	Group	-0.278	0.205
Hematocrit	Month	0.534	<0.001*
Hematocrit	Group × Month	1.454	<0.001*
Hematocrit	Age	-0.001	0.928
Hematocrit	Weight	0.005	0.622
Hematocrit	DM	0.117	0.468
Hematocrit	Baseline value	0.372	<0.001*
Weekly EPO dose	Group	227.026	0.401
Weekly EPO dose	Month	-177.264	<0.001*
Weekly EPO dose	Group × Month	-712.614	<0.001*
Weekly EPO dose	Age	0.516	0.970
Weekly EPO dose	Weight	1.315	0.936
Weekly EPO dose	DM	91.760	0.711
Weekly EPO dose	Baseline value	394.158	0.316
ERI	Group	0.533	0.227
ERI	Month	-0.647	<0.001*
ERI	Group × Month	-1.795	<0.001*

EIR	Age	0.007	0.738
ERI	Weight	-0.261	<0.001*
ERI	DM	0.067	0.865
ERI	Baseline value	-0.463	0.461

β=adjusted regression coefficient, CI=confidence interval, Erythropoietin=EPO, Erythropoietin Resistance Index=ERI, Diabetes Mellitus=DM, *p-value <0.05 was considered statistically significant
The month was entered as the number of months after Month 1. Patient identity was included as a random intercept. Models were adjusted for age, weight, diabetes mellitus status, and the baseline value of the corresponding outcome.

Figure 1 shows the trend in weekly erythropoietin dose from Month 1 to Month 6 in both groups. In the levocarnitine group, the erythropoietin dose decreased steadily over time. In the control group, the erythropoietin dose showed only a slight reduction. The gap between the two groups became wider each month. By Month 6, the levocarnitine group required a much lower erythropoietin dose than the control group. This pattern supports an association between levocarnitine exposure and a lower erythropoietin requirement over time; however, because inflammatory status, dialysis adequacy at follow-up, and transfusion history were not systematically analyzed, the observed difference should be interpreted with caution.

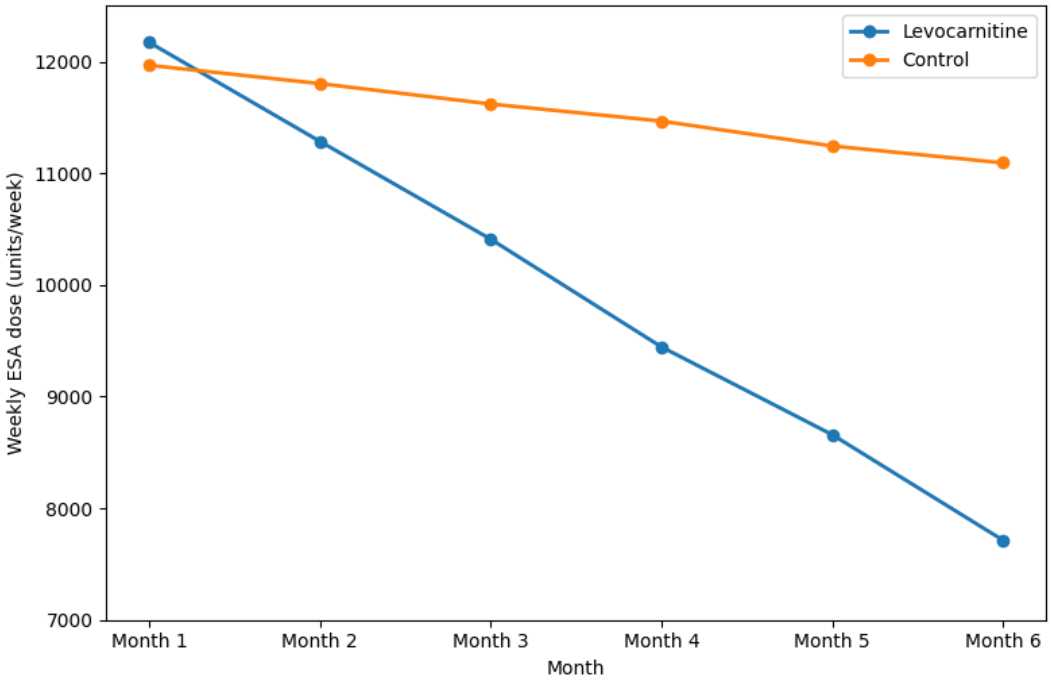

Figure 1: Weekly erythropoietin dose over time in the Levocarnitine and Control groups. Values represent mean weekly erythropoietin dose (units/week) from Month 1 to Month 6

DISCUSSION

In this prospective cohort, adjunctive IV levocarnitine was associated with better anemia-related outcomes in MHD patients over six months. The main findings were higher Hb and Hct, lower weekly EPO dose, and lower ERI in the levocarnitine group compared with the control group. These findings are clinically relevant because anemia control in MHD is affected by several modifiable and non-modifiable factors. Local data from Pakistan have shown that anemia in ESRD patients on HD is associated with PTH level, dialysis-related factors, and other clinical variables, which supports the need to interpret anemia response as a multifactorial outcome rather than as the effect of a single drug alone.[9]

In the present study, Hb increased progressively in the levocarnitine group and became significantly higher than the control group from Month 2 onward. This finding is consistent with national data showing that anemia remains frequent among ESRD patients receiving MHD in Pakistan, which highlights the need for adjunctive approaches that can improve Hb control.[10] Regional evidence from Iran showed a different result, where Sheikhi et al. found no significant post-treatment difference in Hb between patients receiving EPO alone and those receiving EPO with L-carnitine.[11] The difference may be explained by smaller sample size, younger study population, treatment-route differences, and shorter or less consistent exposure to carnitine therapy. Therefore, the Hb finding in the present study supports a possible

beneficial association of IV levocarnitine with anemia correction, but it should not be interpreted as definite proof of causality.

In the present study, Hct followed the same direction as Hb and became significantly higher in the levocarnitine group from Month 2 onward. This parallel rise is biologically plausible because Hct usually increases when red-cell mass improves after effective anemia treatment. A regional randomized trial on another anti-inflammatory adjunct, pentoxifylline, also showed that Hb improved in HD patients, although the between-group Hb difference was not statistically significant.[12] This suggests that adjunctive treatment may help anemia indices in selected HD patients, but the magnitude of benefit depends on the mechanism, study duration, baseline inflammation, and anemia-management protocol. A study from Egypt comparing darbepoetin alfa with epoetin alfa also showed that anemia indices can improve when erythropoiesis support is optimized in HD patients.[13] Therefore, the Hct result in the present study is consistent with the Hb trend and supports improved anemia control in the levocarnitine group.

In the present study, weekly EPO dose decreased steadily in the levocarnitine group and became significantly lower than the control group from Month 3 onward. This finding supports the possible EPO dose-sparing role of IV levocarnitine. International cohort data have shown that EPO response in MHD patients varies with clinical and laboratory factors, so a lower EPO requirement should be interpreted alongside patient condition and baseline risk.[14] Another HD study reported that ultrafiltration rate was related to Hb level and EPO response, which indicates that dialysis-related factors may also influence the need for EPO.[15] Iron handling is another important issue because iron indices and PTH have been linked with ERI in HD patients.[16] Therefore, the lower weekly EPO dose in the levocarnitine group is clinically meaningful, but unmeasured iron kinetics, dialysis adequacy, and inflammatory status may have contributed to the observed difference.

In the present study, ERI decreased progressively in the levocarnitine group and became significantly lower than the control group from Month 3 onward. This finding suggests better EPO responsiveness in patients receiving IV levocarnitine. A study by Zhang et al. showed that higher neutrophil-to-lymphocyte ratio was associated with worse EPO responsiveness in maintenance HD patients, supporting the role of inflammation in ERI.[17] Oxidative stress has also been reported as a contributor to EPO resistance in HD patients, which provides a plausible biological explanation because levocarnitine may improve mitochondrial energy metabolism and reduce oxidative injury.[18] Nutritional status may also affect ERI, as malnutrition has been associated with EPO resistance in patients with end-stage kidney disease.[19]

Body composition is another relevant factor because lower lean tissue mass has been linked with higher EPO resistance in MHD patients.[20] Metabolic syndrome, low albumin, high ferritin, and high hsCRP have also been identified as predictors of EPO resistance in HD patients.[21] Regional variation in EPO hyporesponsiveness has been reported in dialysis populations, showing that patient profile and practice pattern can influence anemia response.[22] A multicenter study comparing darbepoetin alfa with epoetin alfa also supports that treatment regimen and dosing strategy can affect Hb maintenance in dialysis-related anemia.[23] Therefore, the ERI reduction in the present study is plausible, but it should be interpreted as improved EPO responsiveness associated with levocarnitine rather than as a confirmed independent treatment effect.

The present findings are consistent with studies showing that anemia response in HD patients is influenced by treatment strategy, inflammation, nutrition, iron status, PTH level, and dialysis-related factors. The findings differ from the regional L-carnitine study by Sheikhi et al., where no significant Hb improvement was observed. The most likely reasons are differences in sample size, route of carnitine administration, treatment duration, patient age, baseline anemia status, EPO protocol, dialysis adequacy, and unmeasured inflammatory or nutritional factors. Overall, the direction of the present findings supports the conclusion that adjunctive IV levocarnitine was associated with improved anemia indices and reduced EPO requirement over six months in MHD patients.

CONCLUSION

Adjunctive intravenous levocarnitine was associated with reduced erythropoietin requirements and improved anemia indices over six months in maintenance hemodialysis patients.

LIMITATIONS AND FUTURE RECOMMENDATIONS

Several limitations should be acknowledged. The study was single center and non-randomized, with a modest sample size and a six-month follow-up. Levocarnitine use was based on clinical decision rather than random allocation, which introduces the possibility of selection bias and confounding by indication. Although adjusted analysis was performed for measured baseline differences, unmeasured variables may still have affected hemoglobin response and erythropoietin requirement. Important time-varying determinants, including C-reactive protein, follow-up Kt/V, transfusion events, detailed iron

indices, parathyroid hormone control, nutritional status, and carnitine levels, were not systematically included in the analytic dataset. Therefore, the results should be interpreted as an association between adjunctive levocarnitine and improved anemia indices with reduced erythropoietin requirement, rather than definitive evidence of a causal treatment effect.

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