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Intradialytic hypotension frequency is reduced by levocarnitine supplementation

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ABSTRACT

Introduction: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis. IDH causes intradialytic discomfort and subclinical ischemia, resulting in a higher rate of morbidity and mortality. Levocarnitine (LC) administration has been suggested for the treatment of IDH, but conflicting reports about its efficacy have been published. We describe the effect of LC supplementation in patients experiencing recurrent IDH episodes, in spite of common strategies used to prevent it.

Methods: Sixteen hemodialysis patients were studied. IDH was defined as a drop in systolic blood pressure ≥20 mmHg, with or without symptoms, prompting an intervention by the dialysis staff, such as reducing/stopping ultrafiltration rate and/or fluid administration. Blood pressure was recorded for 192 hemodialysis sessions, before LC supplementation. Thereafter LC (30 mg/kg dry weight) was administered at the beginning of each hemodialysis, registering blood pressure for 384 hemodialysis treatments. The difference between the predialysis systolic blood pressure and the minimum systolic blood pressure of each hemodialysis was evaluated (ΔSBP), before and after LC supplementation. Cardiac ejection fraction was also measured.

Results: Predialysis and postdialysis systolic, diastolic, and mean arterial pressures did not differ before and after LC supplementation. Before LC supplementation, 36 episodes of IDH occurred (19%), while after LC supplementation, the IDH episodes were 29 during 384 hemodialysis sessions (8%; $\chi^2 = 16.03$; $p = 0.0001$). ΔSBP was lower after LC supplementation, even though the difference was not significant ($p = 0.22$).

Conclusion: IDH frequency was significantly reduced by predialysis LC supplementation, which can be helpful for patients' well-being and reduction in IDH-associated risks.

Keywords: Carnitine, Hemodialysis, Intradialytic hypotension

Introduction

Intradialytic hypotension (IDH) is one of the most frequent complications of hemodialysis. Preventive strategies for IDH include regular review of dry weight; dietary fluid and salt restriction in order to minimize interdialytic weight gain; optimizing dialysate composition; cooling the dialysate; prohibiting food ingestion during hemodialysis; reassessment of antihypertensive medications; longer/more frequent dialysis treatment time. However, some patients remain prone to IDH. IDH reported prevalence ranges between 7% and 40% of hemodialysis sessions and varies depending on patient characteristics and which definition of IDH is used (1,2). IDH results in unpleasant symptoms such as abdominal discomfort; yawning; sighing; nausea or vomiting; muscle cramps; restlessness; dizziness; or fainting (3). Apart from intradialytic discomfort, IDH brings about subclinical ischemia in various organs, especially heart and brain, resulting in chronic organ dysfunction (4,5), ending in a higher rate of morbidity and mortality (6-8).

Carnitine has an important role in fatty acid metabolism and modulates the resulting adenosine triphosphate (ATP) mitochondrial energy production. Dialysis patients are known to be deficient in levocarnitine (LC), and its supplementation has been proposed to improve cardiac and vascular smooth muscle function, owing to stimulation of heart glucose oxidation (9). In relation with these effects, LC administration has been suggested for the treatment of patients with recurrent symptomatic intradialytic hypotensive events (10-12). However, conflicting and uneven reports about the efficacy of LC on IDH have been published (13). In the present study we describe 16 hemodialysis patients experiencing recurrent

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intradialytic hypotensive episodes, in spite of common strategies used to prevent IDH. LC supplementation was introduced in their treatment schedules to verify its capability in preventing, or at least reducing, the number of intradialytic hypotensive events.

Materials and methods

We observed 16 hemodialysis patients, regularly attending their scheduled hemodialysis sessions, thrice a week. All of them had received hemodialysis for at least 6 months and had experienced two or more IDH episodes in the past 6 months. None of them had ever received LC in the previous 6 months. IDH occurrence was defined as a drop in systolic blood pressure ≥20 mmHg with or without the presence of the above-mentioned symptoms, prompting an intervention carried out by the dialysis staff, such as reducing/stopping ultrafiltration rate and/or fluid administration (11,14).

Blood pressure measures were recorded for 4 weeks, for a total of 192 hemodialysis treatments. Following basal observation period, LC was administered at the beginning of each hemodialysis session, at a dose of 30 mg/kg dry weight, registering blood pressure values for 8 weeks, for a total of 384 hemodialysis treatments. Furthermore, the difference between the predialysis systolic blood pressure and the minimum systolic blood pressure of each hemodialysis was evaluated (ΔSBP), before and after LC supplementation.

During the pretreatment time, patient cardiac function was studied with echocardiography measuring ejection fraction. Demographic information and comorbidities (diabetes, hypertension) were obtained from individual medical records. Laboratory data were routinely scheduled every month. The primary outcome was the number of IDH episodes.

All patients were dialyzed with bicarbonate dialysis, thrice weekly, for 4 hours, with the medium cutoff polyarylethersulfone and polyvinylpyrrolidone Theranova dialyzer (Baxter, Heichingen, Germany). The blood flow rate was 300 mL/min, dialysate flow rate was 500 mL/min, dialysate temperature used was 36.0°C or lower, according to patient's tolerance. The dialysate composition was: sodium 138 mmol/L, potassium 2.0 mmol/L, calcium 1.5 mmol/L, bicarbonate 34 mmol/L, acetate 3 mmol/L, glucose 1 g/L. Throughout the study, no change occurred in hemodialysis prescription, individual dry weight and pharmacological treatment.

Numerical comparisons were performed using Student's *t*-test. Categorical variables were compared using χ^2 test. Statistical analysis was performed using the Statistical Package for the Social Sciences, SV release 6.0 (SPSS, Chicago, IL, USA).

Results

Demographic and clinical characteristics of patients are shown in Table I. Predialysis and postdialysis systolic, diastolic and mean arterial pressure did not differ before and after LC supplementation (Tab. II). During the 4 weeks of basal observation, 36 episodes of IDH occurred throughout 192 hemodialysis treatments (19%). After LC supplementation, the IDH episodes were less frequent and 29 events during

TABLE I - Demographic characteristics of patients

Female/male	9/7
Age, years	68 ± 15
Dry weight, kg	75 ± 17
AVF/permanent catheter	10/6
Sessions/week	3
DM, n (%)	6 (38%)
Hypertension, n (%)	3 (18%)
UFR max, mL/kg/h	<13
Hb, g/dL	10.8 ± 1.6

AVF = arteriovenous fistula; DM = diabetes mellitus; Hb = hemoglobin; UFR = ultrafiltration rate.

TABLE II - Blood pressure metrics before and after LC supplementation

	Before LC supplementation	**After LC supplementation**
	Mean ± SD Median Range Interquartile range	
Predialysis SBP	113 ± 19 109 80-166 99-125	113 ± 17 110 77-176 102-123
Predialysis DBP	60 ± 11 60 34-95 53-66	60 ± 10 60 31-96 54-66
Predialysis MAP	77 ± 12 75 58-117 68-84	78 ± 11 77 55-116 71-83
Postdialysis SBP	110 ± 13 110 70-145 102-119	111 ± 12 111 82-147 104-118
Postdialysis DBP	60 ± 10 60 30-89 54-67	61 ± 11 61 30-90 55-69
Postdialysis MAP	77 ± 9 77 51-101 70-83	78 ± 9 78 56-103 72-84

DBP = diastolic blood pressure; LC = levocarnitine; MAP = mean arterial blood pressure; SBP = systolic blood pressure; SD = standard deviation.

384 hemodialysis treatments were recorded, corresponding to 8% (χ^2 = 16.03; p = 0.0001) (Tab. III). ΔSBP was lower after LC supplementation, even though the difference was not significant in comparison with baseline measurements (p = 0.22) (Tab. IV). Two out of 16 hemodialysis patients suffered from reduced cardiac ejection fraction (45% and 32%, respectively), but no difference in number or frequency of IDH was found when compared with subjects with preserved cardiac ejection fraction (data not shown).

TABLE III - Number (%) of hemodialysis sessions with (IDH positive) and without (IDH negative) intradialytic hypotension, before and after LC supplementation

	IDH positive (n; %)	IDH negative (n; %)
Before LC supplementation	36 (19%)	156 (81%)
After LC supplementation	29 (8%) *	355 (92%)

IDH = intradialytic hypotension; LC = levocarnitine.
* χ^2 = 16.03; p=0.0001.

TABLE IV - Difference between predialysis SBP and the minimum SBP of each hemodialysis (ΔSBP)

	Before LC supplementation	After LC supplementation
ΔSBP		
Mean ± SD	16 ± 7	13 ± 5
Median	15	12
Range	10-39	10-29
Interquartile range	14-21	12-18

LC = levocarnitine; SBP = systolic blood pressure; SD = standard deviation.

Discussion

In this study LC administered intravenously prior to each hemodialysis session significantly reduced IDH episodes. Previous clinical trials reported conflicting results, making studies difficult to compare due to definition of IDH, dose and route of administration of LC or differences in the observed population (13). Since definite sound evidences are uncertain so far, LC supplementation is still underrated in hypotension-prone hemodialysis patients (15). However, our results are in agreement with previous reports, which showed a remarkable and significant risk reduction in preventing and suffering from IDH (10,16). Carnitine deficiency is well known in hemodialysis population and its deficiency has been involved in a variety of complications, such as fatigue, weakness, lipid metabolism, muscle cramps, anemia, hypotension and cardiomyopathy. The hemodynamic mechanism of LC action may be related to an improvement in vascular and cardiac muscle functioning and the stronger cardiac contractility probably brings about the positive vasoactive effects (9,17). In our series only two subjects suffered from reduced cardiac ejection fraction and no correlation could be inferred on the potential usefulness of LC supplementation in myocardial functions.

This complication is still one of the most distressing experiences for hemodialysis patients, but its minimization and prevention go beyond the bounds of intradialytic well-being. Actually, it has been shown that the frequency of minimum systolic blood pressure <90-100 mmHg in serial dialysis sessions significantly increased the risk of mortality, likely related to organ ischemia (18). The main limitation in our study is the number of patients evaluated, although comparable to similar papers (10).

In spite of various prevention strategies being set in motion (low dialysate temperature, increased dialysis time or frequency, pharmacologic therapies), IDH continues to challenge nephrologists and nursing staff attending hemodialysis patients. Considering its safety and lack of adverse effects, LC supplementation is worth trying for patient well-being and reduction in morbidity and mortality risk associated with IDH.

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