



INFLUENCE OF RATE OF ULTRA-FILTRATION AND L-CARNITINE ON INTRA DIALYTIC HYPOTENSION ON REGULAR HEMODIALYSIS PATIENTS

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Abstract

Background: Despite recent advances in dialysis techniques, the high mortality of end-stage renal disease (ESRD) patients remains a major challenge, with most patients depending on haemodialysis (HD) to replace renal function. Intradialytic hypotension (IDH) is one of the most common complications of HD in clinical practice due to the older average age of dialysis patients and the increasing prevalence of comorbidities such as diabetes mellitus and heart failure (HF). The aim of our study was to assess influence of Rate of ultra-filtration and L- carnitine on Intra dialytic hypotension on Regular Hemodialysis Patients.

Methods: Our sample consist of 84 patient we divide them into 2 sub-groups Group1: 42 patients. Group2: 42patient (placebo). Group1 divided into: O L Carnitine group 11 patient. O NA and Temperature group 21patient (A:7 B:7 C:7). O WT based UF group10 patient. Group2 divided into: P1 11 patient. P2 21patient (A:7 B:7 C: 7). P3 10 patient. All sub groups were monitored for 6 months. In order to know the effect of l-carnitine in each hemodialysis session, changing dialysate NA and Temperature during hemodialysis session, WT based Ultrafiltration on reducing rate of IDH on regular hemodialysis patients we choose patients regular attending hemodialysis sessions and not taking any anti-hypertensive medications. In this paper we studied only Rate of ultra-filtration and L- carnitine.

Results: We found insignificant between pre and post in LC group as regard SBP and BP (mmHg). We found regarding UF There is statistically significant difference between the studied groups regarding systolic and diastolic blood pressure after two hours and by the end. There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline.

Conclusion: Regarding UF There is statistically significant difference between the studied groups regarding systolic and diastolic blood pressure after two hours and by the end. There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline.

Keywords: Noradrenaline, terlipressin, and hepatorenal syndrome

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1. INTRODUCTION

Intradialytic hypotension (IDH) is common complication in stage 5 chronic kidney disease patients on hemodialysis. Incidence ranges from 15 to 30% (1).

The European Best Practice Guideline (EBPG) on hemodynamic instability defines the IDH as a decrease in systolic blood pressure (SBP) by ≥ 20 mm Hg or a decrease in mean arterial pressure (MAP) by ≥ 10 mm Hg associated with a clinical event and the need for a nursing intervention (2).

Improvement of patients undergoing hemodialysis HD depends on not only medicines but also diet and fluid restrictions. Failure to comply with such restrictions is associated with complications such as fluid retention, accumulation of toxic substances

cardiovascular problems, and ultimately premature death. (3)

Patients with ESRD undergoing hemodialysis (HD) are at greater risk of cardiovascular (CV) disease-related morbidity and mortality compared with the general population, with published estimates suggesting that the differential risk is as high as 8- to 20-fold (4).

There is increasing evidence implicating IDH in the pathophysiology of “uremic cardiomyopathy.” Intradialytic hypotension increases the risk of myocardial hypoperfusion, leading to segmental ischemia inducing segmental left ventricular dysfunction. A process known as myocardial stunning. Myocardial stunning is cumulative and leads to irreversible left ventricular dysfunction in ischemic heart disease (5).

Sodium modeling is a technique in which the dialysate sodium concentration is varied during the course of the hemodialysis procedure. Most is used initially with a progressive reduction toward isotonic or even hypotonic levels by the end of the procedure. This method of sodium control allows for a diffusive Na influx early in the session to prevent the rapid decline in plasma osmolality as a result of the efflux of urea and other small molecular weight solutes. During the remainder of the procedure, when the reduction in osmolality accompanying urea removal is less abrupt, the dialysate sodium level is set at a lower level (6).

L-Carnitine (LC) is synthesised in tissues from lysine and methionine. It is an essential cofactor for the transfer of long-chain fatty acids to mitochondria. In the higher mammals its recycling is highly efficient, more than 90% of filtered L-carnitine being re-absorbed by the kidneys at normal physiological plasma concentrations and it is well established that chronic renal insufficiency patients undergoing regular dialysis treatment suffer from serum carnitine deficiency. The suggested causes being either the loss of considerable quantities of carnitine during dialysis or diminished endogenous synthesis of carnitine (7).

Fluid extraction by ultrafiltration results in a sudden fluid compartment change that causes BP instability. The UFR is a key predisposing factor to IDH, especially when it exceeds the plasma refill rate, with the risk for IDH increasing greatly with increasing gaps between UFR and plasma refill. Higher UFR (>10→13 mL/h/kg in different studies) were consistently associated with a higher incidence of IDH and mortality. The rapid loss of volume overwhelms the compensatory mechanisms and the plasma refilling and venous return lag behind. Autonomic dysfunction or decreased contractility disrupt the compensatory mechanisms even further, thus patients with chronic heart failure (CHF) tend to develop IDH with lower UFRs. Therefore, reducing the UFR either by increasing the time or frequency of dialysis sessions tends to decrease the occurrence of IDH. On top of the UFR, rapid clearance of waste products during HD may lead to the formation of transient osmotic gradients, causing water loss from the extracellular to the intracellular space. (8).

Cool dialysate reducing the temperature of the dialysate below the core body temperature is one of the most-used preventive methods against IDH. In fact, European Best Practice Guidelines (EBPGs) recommend the use of cool dialysate as a first-line option to prevent IDH. Cool dialysate decreases the risk of IDH development by inducing vasoconstriction and activating the sympathetic nervous system (9).

The aim of our study was to assess influence of Rate of ultra-filtration and L- carnitine on Intra

dialytic hypotension on Regular Hemodialysis Patients.

2. PATIENTS AND METHODS

A) Clinical trial study was carried out in Met Ghamr hospital of Nephrology and Urology.

B) **Sample size:** Assuming that percentage of Intra dialytic hypotension (IH) in l-carnitine group 13.3% and in placebo group 43.3% so the sample size will be 84(42 in each group) using epi info power 80% CI 95% (10).

Inclusion criteria

- o men and nonpregnant women
- o not breastfeeding
- o aged 18 to 85 years
- o regular attendance to hemodialysis sessions
- o at least twice a week; spent the previous 6 months on hemodialysis treatment
- o patients who had two or more IDH episodes in the past 6 months not taking high blood pressure medications.

Exclusion criteria

- o septic history in the previous 6 months
- o pregnancy
- o Lactation
- o history of hypersensitivity or contraindication to LC
- o Patients with malignant disease
- o Patients with advanced cardiovascular disease
- o Shock
- o Patients with active infection

All patients included in this study will be subjected Through history taking with special regard to comorbidity, drug history and dialysis frequency.

Complete clinical examination with special emphasis on blood pressure (pre- and post-dialysis) and body weight, Levocarnitine supplementation before each hemodialysis session, dialysate NA and T.

Changes on dialysis machine dialysate temperature 36°C, sodium dialysate concentration at the beginning of HD will be 140mmol/L, which will be decreased linearly every hour until it reach 135 mmol/L in the last hour of dialysis session.

Weight based ultra-filtrate 13 mL/kg/h.

We divide sample into 3groups to study the effect of l carnitine, changes to dialysate NA, temperature, wt based ultrafiltration on IDH on regular hemodialysis patients .

- o L Carnitine group 11 patient, 11 patient placebo
- o NA and Temperature group 21patient, 21patient placebo
- o WT based UF group 10 patient and 10 patient placebo

In this paper we studied only Rate of ultra-filtration and L- carnitine.

All enrolled patients signed informed consent. The protocol trial was approved by Zagazig University

Institution Review Broad and Internal medicine department.IRB

L Carnitine group:

L Carnitine group (LC) 11 patient, 11 patient placebo (P).

Patients were randomized into the levocarnitine group and placebo group.

❖LC group was administered at a dose of 30 mg/kg per session (three sessions/week).

❖P group normal saline, 5 mL/session, three sessions/week)

Both groups administered as slow intravenous bolus (2–3 min) through the venous line, before each session of hemodialysis, respectively and accordingly to the allocated group.

Blood pressure of every enrolled patient was assessed using a conventional sphygmomanometer at the begin of the session, 2nd hour of session and at the end of the session.

Hemodialysis settings:

❖All patients were dialyzed with bicarbonate dialysis

❖Thrice weekly for 4 h with a poly ethaline high flux hollow-fiber dialyzer FRESSNUS4008s hemodialysis machine

❖The blood flow rate was 350

❖dialysate flow rate was 500 mL/min, -

❖dialysate temperature used was 36.5°C, all were kept constant throughout the study period.

❖The dialysate composition was: sodium 138 mmol/L, potassium 2 mmol/L, calcium 1.75 mmol/L, bicarbonate 32 mmol/L, acetate 3 mmol/L, glucose 1 g/L, Mg, 50 mmol/l, Cl 109,5

WT based ultrafiltration

WT based UF group 10 patient and 10 patient placebo

The UF rate limit was initiated in this dialysis facility. The rate limit of 13 mL/kg/h was chosen as the UF rate threshold.

The patients were verbally notified of the upcoming UF rate limit policy beginning 4 weeks prior to the change, then given a written letter with the policy 2 weeks prior. They were reminded of their current prescribed treatment time and informed how much fluid weight could be removed during that time using the

UF rate limit of 13 mL/kg/h. For example, a 70-kg man with a 4-hour treatment time could have a maximum of 13 mL/kg/h x 70 kg x 4 hours = 3640 mL removed during that treatment.

Statistical analysis

The collected data will be, tabulated, and statistically analyzed using

SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016

Descriptive statistics were done for numerical parametric data as mean ± SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median and

1st & 3rd inter-quartile range, while they were done for categorical data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non-parametric data. Inferential analyses were done for qualitative data using Chi square test for independent groups. Wilcoxon Rank test was used to assess the statistical significance of the difference of a non - parametric variable between related sample. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

3. RESULTS

Our sample consist of 84 patient we divide them into 2 sub groups

Group1 42 patient

Group2 42 patient (placebo)

Group1 divided into

O L Carnitine group 11 patient

O NA and Temperature group 21 patient (A:7 B:7 C:7)

O WT based UF group 10 patient

Group2 divided into

P1 11 patient

P2 21 patient (A:7 B:7 C:7)

P3 10 patient

Table (1) shows demographic characteristics among the two studied groups. The mean age 47.57 ± 11.91 in group 1, The mean age 47.59 ± 10.93 in group 2. There were 46.7% smoker, 16.67% with Stoppage of the S. habits during and after TTT. There were no significant difference between both groups as regard demographic characteristics.

Table (2) shows Lab characteristics among the studied groups. The mean Pre urea 131.44 ± 13.20 in group 1, The mean Pre urea 102.21 ± 10.45 in group 2. The mean post urea 40.45 ± 5.21 in group 1, The mean post urea 42.21 ± 5.63 in group 2. The mean Ca 9.92 ± 1.3 in group 1, The mean Ca 9.82 ± 1.1 in group 2. The mean Ph 5.21 ± 1.3 in group 1, The mean Ph 5.21 ± 1.3 in group 2. The mean Pre-dialysis Creatinine 9.81 ± 2.21 in group 1, The mean Pre-dialysis Creatinine 9.9 ± 2.4 in group 2. There were high significant between pre and post in group 1 as regard urea. There were high significant between pre and post in group 2 as regard urea

Figure (1) shows BP characteristics among the two studied groups. The mean Pre-HD SBP 132.2 ± 18.0 in group 1, The mean Pre-HD SBP 131.1 ± 16.20 in group 2. The mean Pre-HD DBP 81.81 ± 9.12 in group 1, The mean Pre-HD DBP 80.52 ± 8.44 in group 2. The mean Post -HD SBP 121.98 ± 11.88 in group 1, The mean Post -HD SBP 129.86 ± 11.96 in group 2. The mean Post -HD DBP 72.90 ± 5.18 in

group 1, The mean Post -HD DBP 76.88±5.32 in group 2.

The mean Change in SBP -11.12±9.26 in group 1,

The mean Post -HD SBP -3.55±5.23 in group 2.

The mean Change in DBP -9.23±6.88in group 1,

The mean Change in -HD DBP -2.65±5.10 in group 2.

There were high significant between pre and post in group 1.as regard SBP and DBP (mmHg). There were high significant between pre and post in group 2 as regard DBP (mmHg)

There were high significant difference between both groups as regard Change in SBP (mmHg)

Table (3) shows BP characteristics among L-Carnitine (LC) group and placebo group (P). . The mean Pre-HD SBP 130.2±17 in group LC, The mean Pre-HD DBP 130.1±16.89 in group LC. The mean Post -HD SBP 120.23±11.21 in group LC, The mean Pre-HD DBP 72.89±5.20 in group LC

The mean Pre-HD SBP 130.1±16.89 in group P, The mean Pre-HD DBP 79.20±8.23 in group P.

The mean Post -HD SBP 128.86±11.25 in group P,

The mean Pre-HD DBP 76.78±5.30 in group P

There were high insignificant between pre and post in LC group as regard SBP and DBP (mmHg).

There were high insignificant between pre and post in p group as regard SBP and DBP (mmHg)

Table (4) shows There is statistically significant difference between the studied groups regarding

systolic and diastolic blood pressure after two hours and by the end. There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline

Table (5) shows There is statistically significant difference between the studied groups regarding UF profiling after 2 hours and by the end. There is statistically non-significant difference between the studied groups regarding UF profiling baseline.

There is statistically non-significant difference between the studied groups regarding gender or age Table (6).

There is statistically significant difference between the studied groups regarding systolic and diastolic blood pressure after two hours and by the end. There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline Table (7).

There is statistically significant difference between the studied groups regarding UF profiling after 2 hours and by the end. There is statistically non-significant difference between the studied groups regarding UF profiling baseline Table (8).

There is statistically significant difference between the studied groups regarding cramps, headache and dizziness (significantly higher among placebo group) Table (9).

Table (1):Demographic characteristics among the studied groups

		Group 1 (n = 42)		Group 2 (n = 42)		Test value	P-value
		N	%	N	%		
Sex	Male	23	54.7%	28	66.67%	X ² = 1.24	0.26
	Female	19	45.2%	14	33.33%		
Age		47.57 ± 11.91		47.59±10.93		1.21	0.54
Dialysis frequency per week		3.2 ± 0.4		3.22 ± 0.44			
BMI		26.22±4.96		26.45±4.86			

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation, ZMWU = Mann-Whitney U test, X²= Chi- Square test

Table (2):Lab characteristics among the studied groups

		Group 1 (n = 42)	Group 2 (n = 42)	Test value	P-value
urea	Pre	131.44±13.20	102.21±10.45	1.59	0.13
	Post	40.45±5.21	42.21±5.63	1.16	0.62
		^a p=0.00001	^b p=0.001		
Ca		9.92±1.3	9.82±1.1	1.3	0.28
Ph		5.21±1.3	5.44±1.32	1.031	0.92
Pre-dialysis Creatinine		9.81±2.21	9.9±2.4	1.179	0.59

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation, ZMWU = Mann-Whitney U test ap≤ 0.05= significant between pre and post in group 1. bp≤ 0.05= significant between pre and post in group 2.

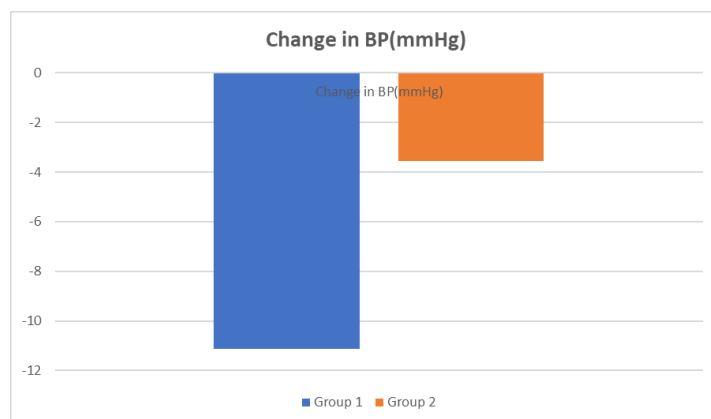


Fig. (1): BP among the studied groups

Table (3):BP characteristics among L-Carnitine(LC) group and placebo group (P).

		LC Group (n = 11)	P Group (n = 11)	Test value	P-value
Pre-HD BP(mmHg)	SBP	130.2±17.9	130.1±16.89	1.12	0.85
	DBP	80.45±9.12	79.20±8.23	1.22	0.75
Post-HD BP (mmHg)	SBP	120.23±11.21	128.86±11.25	1.00	0.99
	DBP	72.89±5.20	76.78±5.30	1.03	0.95
SBP		^a p=0.15	^b p=0.21	-	-
DBP		^a p=0.09	^b p=0.18	-	-

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation, ZMWU = Mann-Whitney U test. ap≤ 0.05= significant between pre and post in group 1. bp≤ 0.05= significant between pre and post in group 2.

Table (4):Comparison between UF group and Placebo group regarding blood pressure over time of session:

	UF group (n = 10)	Placebo group (n = 10)	t	P-value
Systolic blood pressure	Mean ±SD	Mean ±SD	t	P
Baseline	100.0 ±18.71	108.0 ±8.37	-0.873	0.408
After 2 hours	110.0 ±7.07	94 ±11.4	2.667	0.029
End	114.0 ±5.48	92 ±8.37	4.919	<0.001
Diastolic blood pressure				
Baseline	68 ±8.37	78 ±8.37	-1.89	0.095
After 2 hours	78 ±6.71	64 ±9.62	2.67	0.028
End	80 ±6.12	56 ±4.18	7.236	<0.001

Table (5):Comparison between UF group and Placebo group regarding UF profiling

	UF group (n = 10)	Placebo group (n = 10)	t	P-value
Systolic blood pressure	Mean ±SD	Mean ±SD	t	P
Baseline	98.0 ±14.83	114.0 ±11.4	-1.912	0.092
After 2 hours	112.0 ±4.47	94 ±8.94	4.025	0.004
End	112.0 ±8.37	88 ±10.95	3.893	0.005
Diastolic blood pressure				
Baseline	68 ±8.37	78 ±8.37	-1.89	0.095
After 2 hours	81 ±5.48	64 ±5.48	4.097	0.001
End	79 ±7.42	58 ±4.47	5.422	0.001

Table (6):Comparison between UF group and Placebo group regarding demographic data:

	UF group (n = 10)	Placebo group (n = 10)	X ²	P-value
Gender			Fisher	>0.999
Male	6 (60%)	5 (50%)		
Female	4 (40%)	5 (50%)		
	Mean ±SD	Mean ±SD	t	P
Age (year)	44.0 ±7.83	49.3 ±9.56	-1.356	0.192

Table (7):Comparison between UF group and Placebo group regarding blood pressure over time of session:

	UF group (n = 10)	Placebo group (n = 10)	t	P-value
Systolic blood pressure	Mean +SD	Mean +SD	t	P
Baseline	100.0 +18.71	108.0 +8.37	-0.873	0.408
After 2 hours	110.0 +7.07	94 +11.4	2.667	0.029
End	114.0 +5.48	92 +8.37	4.919	<0.001
Diastolic blood pressure				
Baseline	68 +8.37	78 +8.37	-1.89	0.095
After 2 hours	78 +6.71	64 +9.62	2.67	0.028
End	80 +6.12	56 +4.18	7.236	<0.001

Table (8):Comparison between UF group and Placebo group regarding UF profiling:

	UF group (n = 10)	Placebo group (n = 10)	t	P-value
Systolic blood pressure	Mean +SD	Mean +SD	t	P
Baseline	98.0 +14.83	114.0 +11.4	-1.912	0.092
After 2 hours	112.0 +4.47	94 +8.94	4.025	0.004
End	112.0 +8.37	88 +10.95	3.893	0.005
Diastolic blood pressure				
Baseline	68 +8.37	78 +8.37	-1.89	0.095
After 2 hours	81 +5.48	64 +5.48	4.097	0.001
End	79 +7.42	58 +4.47	5.422	0.001

Table (9):Comparison between UF group and Placebo group regarding associated symptoms:

	UF group (n = 10)	Placebo group (n = 10)	X ²	P-value
Cramps Headache dizziness	2 (20%)	9 (90%)	Fisher	0.005*
	2 (20%)		7.2	0.007*
	0 (0%)		Fisher	0.011*
		8 (80%)		
		6 (60%)		

4. DISCUSSION

During 6 months we compare GROUP1 subgroups with Group2 subgroups for rate of IDH. There were high insignificant between pre and post in p group as regard SBP and DBP (mmHg). Our findings are against Ibarra-Sifuentes et al (10) regarding LC before session effect on IDH. In this randomized trial, LC showed beneficial prophylactic effects on IDH episodes when administered intravenously prior to each hemodialysis session. As shown in this trial, we found a 23.9% statistically significant risk reduction in IH episodes in patients receiving intravenous LC before each hemodialysis session compared with those receiving placebo (P < 0.001). In the anecdotal randomized trial in, Ahmad et al (11) demonstrated an IH episode reduction of 44% to 18% in the carnitine group (P < 0.02) when administered intravenously during hemodialysis sessions. In 2007, Lynch et al. (12) in their meta-analysis, cite five clinical studies, showing that LC supplements produced an odds ratio of 0.28 (confidence interval 95%, 0.04–2.23; P = 0.2). Our study shows regarding UF. There is statistically significant difference between the studied groups regarding systolic and diastolic blood pressure after two hours and by the end.

There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline.

SBP P value at Baseline time 0.408
 SBP After 2 hours P value 0.029*
 SBP End P value <0.001**
 DBP Baseline P value 0.095
 DBP After 2 hours P value 0.028*
 DBP End P value <0.001**

In study made by Awad et al (14) this study using of step-down sodium + UF profiles reported significant decrease in the incidence of intradialytic hypotension and related symptoms included, muscle cramps, dizziness and headache and all nursing interventions (saline infusion, decrease or stop UF, session failure) (p<0.001).

Our study shows regarding UF profile. There is statistically significant difference between the studied groups regarding UF profiling after 2 hours and by the end.

There is statistically non-significant difference between the studied groups regarding UF profiling baseline.

SBP P value at Baseline time 0.092
 SBP After 2 hours P value 0.004*
 SBP End P value 0.005*
 DBP Baseline P value 0.095
 DBP After 2 hours P value 0.001**
 DBP End P value 0.001**

Our study show regarding associated symptoms as (Cramps, Headache and Dizziness) There is statistically significant difference between the studied groups regarding cramps, headache and dizziness (significantly higher among placebo group)

Cramps P value 0.005*
Headache P value 0.007*
Dizziness P value 0.011*

Limitations to our study are relative short periode of the study and small number of included patients. we recommend a longer period, multicenter and nationwide study with more emphasis on possible cardiovascular adverse effects of IDH.

5. CONCLUSION

We found regarding UF There is statistically significant difference between the studied groups regarding systolic and diastolic blood pressure after two hours and by the end. There is statistically non-significant difference between the studied groups regarding systolic and diastolic blood pressure baseline.

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