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Minimizing Myocardial Ischemic Injury by Cool Dialysate in Maintenance Hemodialysis Patients: A Randomized Controlled Trial

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ABSTRACT

Background: Emerging evidence supports a cardiovascular protective role of Cooled Dialysis (CD) in incident Hemodialysis (HD) patients. Whether this benefit can be extended to maintenance HD patients remains to be established.

Objective: The aim of the present study was to assess the impact of CD by lowering Dialysate temperature (dt) 0.5ºC below Core Body Temperature (CBT), on minimizing myocardial ischemia in maintenance HD patients (>1 year on HD).

Patients and Methods: from March 2019 to January 2021, we randomized one hundred maintenance HD patients to receive either Cooled Dialysis (dt - 0.5ºC below CBT, intervention) or Standard Dialysis (dt= CBT, control) for 12 months. Over the study period, serial measurements of ECG, echocardiography, and myocardial enzymes (CK-MB and Troponin-T) were performed for the whole study population as surrogates for myocardial ischemic injury.

Results: By the end of 12-months, compared to Standard Dialysis (ST) patients, Cooled Dialysis (CD) patients had overall less incidence of new myocardial ischemia (composite surrogate outcomes: ECG, Echo and CK-MB) (p=0.032). In logistic regression analysis, CD was found to be independently protective against myocardial ischemia (OR 0.54, p-value 0.033, CI: 0.3-0.95). **Conclusion:** In maintenance HD patients, Cooled Dialysis might help decrease myocardial ischemia with a reasonable safety profile. Further studies are warranted to explore these findings.

Keywords: Core Body Temperature (CBT)**,** Cooled dialysate (CD), Dialysate Temperature (dt), Hemodialysis (HD), Ischemia-Reperfusion Injury (IRI).

INTRODUCTION

Cardiovascular disease (**CVD**) is the leading cause of morbidity and mortality among End-Stage Renal Disease (**ESRD**) patients on Hemodialysis (**HD**) [(1)]. Early in the course of Chronic Kidney Disease (**CKD**) with 75% of patients having preexisting CVD, patients are more likely to experience Major Adverse Cardiovascular Events (**MACE**) than to progress to ESRD. As CKD progresses to ESRD, transition from traditional atherosclerotic to nontraditional non-atherosclerotic MACE is noted in HD patients accounting for up to 50% of mortality [(2)].

Emerging evidence has shed light on the dark side of conventional HD which acts as a major "circulatory stressor" in ESKD patients prone to Intradialytic Hypotension (**IDH**). Left untreated, repetitive episodes of IDH further trigger and accelerate CVD by inducing cumulative HD- mediated Ischemia-Reperfusion Injury (**IRI**) [(3)]. Therefore, on its own, conventional HD acts as a cardiovascular "disease modifier" by superimposing ischemic multiorgan injury on preexisting complex comorbidities in this population. Thus, HD, in and of itself, accelerates and augments (CVD) morbidity and mortality [(1-3)].

Over the past decade, HD-induced circulatory stress has been the focus of a series of imaging, and biomarker studies addressing the subclinical insults of (IDH) affecting the vulnerable vascular beds in the heart, brain, kidney, Gut and liver. The cumulative HD-induced IRI ends in myocardial stunning, HD-induced cardiomyopathy, brain white matter ischemia, cognitive dysfunction, decreased renal perfusion and endotoxemia due to disruption of Gut barrier [(3-9)].

Another overlooked factor in the unique profile of CVD in HD patients is the HD-induced "thermal stress" due to the thermal imbalance encountered during HD procedure that further adds to the impaired thermoregulatory mechanisms when they are most needed to combat the "circulatory stress" superimposed by HD [(10)].

Up to 40% of HD patients have dysregulated baseline Core Body Temperature (**CBT**) at low levels of 36.5ºC, hence dialyzing patients against an arbitrarily set 37ºC "standard" dialysate temperature **(dt)** results in passive transfer of heat energy from dialysate to the patient. The end result of this "supraphysiological" heating during HD would be excessive vasodilatation of vasculature which further compromises the hemodynamic responses to IDH. Conversely, Dialysate Cooling (**CD**) has been traditionally employed in HD patients who cannot tolerate ultrafiltration- induced hypovolemia to offset (IDH) based on its favorable hemodynamic stabilizing effect attributed to enhanced cardiac inotropy, improved peripheral vascular resistance, and catecholamine surge induced by lowering dialysate temperature [(11-15)].

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More recently, a series of Randomized Controlled Trials (**RCTs**) have demonstrated that CD has a protective effect against HD-induced ischemic multiorgan injury in incident HD patients individualized for CD including minimizing myocardial stunning, brain white matter ischemia, and Drop in Renal Perfusion (DRP) that occur in patients prone to IDH. These RCTs have advocated innovative imaging modalities and sensitive cardiac biomarkers to demonstrate two simultaneous findings: first: the negative impact of IDH on the progression of ultrastructural (IRI) superimposed by conventional HD, and second: the protective role of CD to delay such ischemic changes in the vulnerable vascular territories [16-18].

However, the previous RCTs have focused on individualizing incident HD patients to CD, therefore, the aim of the current study was to examine whether the cardioprotective benefit of CD could be extended to maintenance HD patients (i.e., with long HD vintage) to minimize the myocardial ischemia using surrogates for myocardial injury including: ECG, echocardiography and cardiac enzymes (CK-MB and Cardiac Troponin T (cTnT)) for monitoring of ischemic events in such vulnerable population.

PATIENTS AND METHODS

From March 2019 to January 2021, we conducted an open label, prospective, randomized-controlled trial (RCT) to test whether dialysate cooling (CD) would help minimize myocardial ischemic injury in maintenance HD patients.

One hundred maintenance HD patient from Benha University Hospital were enrolled in the study. A 1:1 computer-generated sequencing placed in sealed envelopes was used for randomization. Fifty patients were randomly assigned to each treatment arm. Blinding (of the intervention) was not technically feasible because of the need to serially adjust dialysate temperature (td) prescription settings. The study was performed as a parallel RCT; however, crossover was allowed between the treatment arms if clinically indicated as per the treating physician. Data analysis was performed eventually as per original treatment allocation with Intention to Treat (**ITT**) analysis at the end of the trial period. The duration of the study for each subject was 12 months.

Ethical approval:

The study was performed in accordance with the principles and regulations of the Helsinki's declaration. The study protocol was approved by the Ethical Committee of Benha University on 30/1/2019, with approval number 2353/257. All the participants gave an informed written consent in Arabic language fully explaining the study and highlighting the potential hazards and benefits. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Intervention:

The present study used 2 different prescription protocols for dialysate temperature (td):

(1) Intervention arm (50 patients), received cooling of dialysate (CD) to 0.5°C below the pre-dialysis Core Body Temperature (CBT) (dt= CBT - 0.5°C).

(2) Control arm (50 patients), received standard temperature dialysate (ST) to the same degree of patient's Core Body Temperature (CBT) measured before each HD session (dt= CBT).

HD Treatments:

With regards to HD prescription, the average + standard deviation achieved temperature in the CD group was (35.9 ± 0.45) vs (36.5 ± 0.55) in the ST group. The time of sessions, ultrafiltration rates, and achieved URR targets were, overall, similar between groups. Conventional Hemodialysis was delivered to all patients using Fresenius HD4008 B machines, low-flux poly-sulfone dialyzers, bicarbonate-based dialysate. Dialysate composition was almost similar between groups. Core Body Temperature (CBT) was monitored using tympanic membrane thermometer taken at the beginning of HD then serially every hour.

Data collection:

Baseline demographics, clinical and laboratory, and imaging data for the whole study population were initially collected then serial Electrocardiography (ECG), Echocardiography (Echo) and myocardial biomarkers (creatinine kinase-MB and Cardiac Troponin T- cTnT) were obtained regularly on a mid-week day (Either Monday or Tuesday) following the HD session.

Endpoints: In the present study three surrogate markers for new myocardial ischemia were followed from baseline along different time points at (3, 6, 9, and 12 months), namely: (ECG), (Echo) and cardiac enzymes (CK-MB and Cardiac Troponin T- cTnT). We analyzed for the correlation between the intervention (CD vs ST) and the change in each separate surrogate and with the total changes of the composite comprising the three surrogates.

Statistical analysis

The collected data was coded and introduced to a PC using Statistical package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA). Parametric data were presented as mean and standard deviation (± SD), non-parametric data as median and range, and categorical variables as counts (Frequency and percentage). As to the analytical statistics; Student T test was used to assess the statistical significance of the means

values. Mann Whitney test to assess the statistical significance of variable medians and chi-square tests for qualitative variables. McNemar test was used to test for difference for each time point.

Repeated measure ANOVA and ANCOVA (for parametric) or Freidman's test (for non-parametric) variables for comparison of repeated measures across all time points with post-hoc test conducted for multiple comparison. Logistic regression analysis for prediction of risk factors was also used. All *P*-values less than 0.05 were considered significant.

RESULTS

As shown in figure (1), We initially evaluated (138) Maintenance HD patients for enrollment in the study, (38) were ruled out (18 were ineligible and 20 were not interested in the study), (50) patients were randomized to each treatment arm. (6) patients from each arm were re-allocated to the other treatment arm based on the decision of the treating physician. Six patients were re-allocated from ST (Control group) to the CD (Intervention group) due to recurrent IDH, six patients were re-allocated from the CD (Intervention group) to the ST (Control group) due to cold-intolerance.

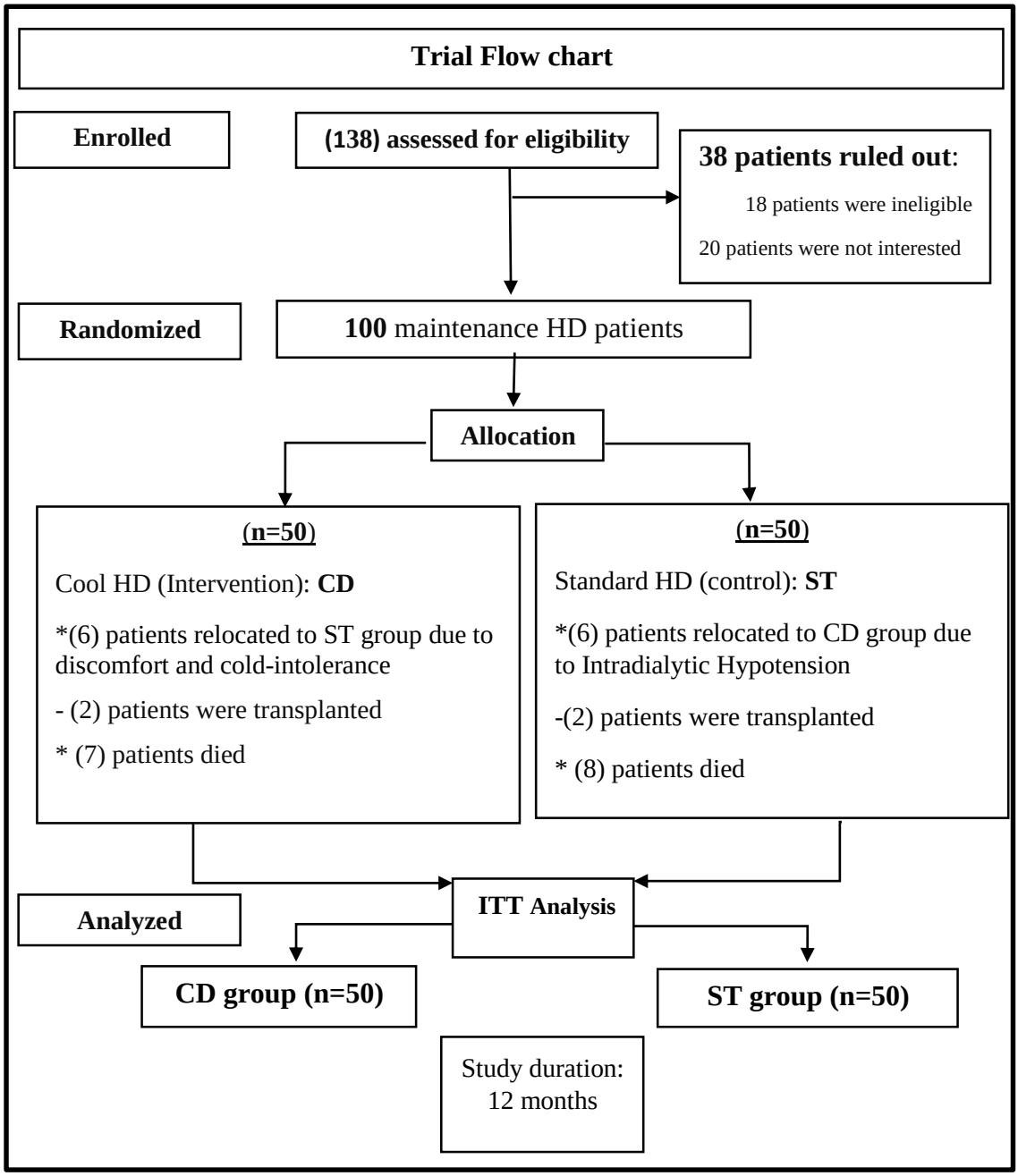


Figure (1). Randomized Controlled Trial flow chart as per CONSORT (Consolidated Reporting of Trials).

As shown in **table 1**, Baseline demographic data did not show significant between- group differences regarding age, sex, BMI or smoking status. Yet, the intervention group were on average 2- years older.

Table (1). Comparison of demographics and general characteristics among both study groups.

			Control group (n = 50)		intervention group (n = 50)		P value
Age (years)	***Median, range**		50	24-70	52	24-65	0.669
Gender	**Males**	**N (%)**	30	60%	32	64%	0.680
	Females	**N (%)**	20	40%	18	36%	
Smoking	**N (%)**		10	20%	14	28%	0.349
BMI (kg/m^2)	***Median, range**		21.4	19.4-27.3	23.3	19.8-26.4	0.113

SD, standard deviation; *non-parametric data were compared using *Mann-Whitney test*; categorical data were compared using chi square test.

As shown in table 2, the control group had a higher frequency of hypertension that was statistically significant compared to the intervention group. There was no statistically significant between-groups difference in the remainder of comorbidities.

Table (2). Comparison of comorbidities among both study groups.

			Control group (n = 50)		intervention group (n = 50)		P value
Hypertension	**Present**	**N (%)**	32	64%	22	44%	**0.045**
	Duration (years)	**Median (range)**	6	0.9-32	5	1-20	0.598
	Controlled	**N (%)**	34	68%	40	80%	0.171
	Uncontrolled	**N (%)**	16	32%	10	20%	
Diabetes Mellitus		**N (%)**	14	28%	18	36%	0.391
Peripheral Vascular Disease		**N (%)**	14	28%	20	40%	0.205
Ischemic Heart Disease		**N (%)**	14	28%	18	36%	0.391

Numerical data are compared using Mann Whitney test; categorical data are compared using chi square test.
As shown in table 3, baseline laboratory values did not differ significantly between both groups ($p>0.05$) except for Hemoglobin and Cholesterol (($p<0.05$).

Table (3). Comparison of baseline laboratory data among both study groups.

Laboratory Value		**Control group (n = 50)**		**intervention group (n = 50)**		**P value**
Hemoglobin (g/dL)	**Mean ±SD**	10.1	±2	9	±1	<0.001
Albumin (g/dL)	**Mean ±SD**	3.6	±0.3	3.5	±0.4	0.161
Cholesterol (mg/dL)	**Mean ±SD**	170.6	±17.5	158	±27.7	<0.01
Calcium (mg/dL)	**Mean ±SD**	8.8	±1.3	8.5	±1.9	0.359
Phosphorus (mg/dL)	**Median, range**	6.6	2.5-8	6.8	2.5-9.9	0.881
PTH	**Median (range)**	315	59-85	322	66-87	0.324
ESR (mm/h)	**Median (range)**	40	10-20	30	9-40	0.156
CRP (g/mL)	**Median (range)**	6.2	3.1-10	6.1	3.3-10.4	0.324
CK-MB (IU/L)	**Median (range)**	6.0	3- 11.2	6.3	3.6-12.1	0.270
Troponin (ng/ml)	**Median (range)**	0.65	0.42-0.8	0.67	0.41-0.8	0.102

Hemoglobin, albumin, calcium, and Cholesterol were compared using **t test**; Phosphorus, ESR, CRP, CK-MB and troponin-T were compared using **Mann Whitney test**.

As shown in **table 4**, the mean achieved dialysate temperature (td) was lower in the intervention group. Otherwise, there was no significant difference in the prescribed HD sessions with regards to Ultrafiltration rates, fluid removed or Intradialytic weight gain.

Table (4). Summary of Haemodialysis (HD) prescriptions.

Characteristic		COOL HD (n = 50)	Standard HD (n = 50)	P Value
Time on HD time (hour)	**Mean ±SD**	4.25 ± 0.25	4.27± 0.31	0.723
Rate of Ultrafiltration (ml/kg/hour)	**Median, range**	9.8 (7.2-11.1)	9.8 (7-11.5)	0.812
Amount of fluid removed	**Mean ±SD**	2.93 ± 0.56	2.92± 0.51	0.926
IDWG (Intradialytic weight gain)	**Median, range**	3.5 (2.1-3.3)	3.4 (2.4-3.6)	0.629
The achieved dialysate temperature (mean)	**Mean ±SD**	35.3 ± 0.45	36.5 ± 0.32	**<0.001**

As shown in table (5), At baseline, no significant differences were found between both groups regarding IDH, while at 3, 6, 9, and 12 months, intervention group (CD) showed significantly lower frequency of IDH (p value < 0.001).

Table (5). Intradialytic Hypotension (IDH) among groups at different follow up points.

		Control group (n = 50)		intervention group (n = 50)		P^1
		N	%	N	%	
At baseline	**Total**	50		50		
	IDH	16	32%	22	44%	0.216
After 3 months	**Total**	50		50		
	IDH	18	36%	8	16%	**0.023**
At 6 months	**Total**	50		46		
	IDH	16	32%	2	4.3%	**<0.001**
At 9 months	**Total**	48		46		
	IDH	14	29.2%	2	4.3%	**0.001**
At 12 months	**Total**	46		46		
	IDH	12	26.1	2	4.3%	**0.004**
	P2	0.615		**<0.001**		
	P3	**<0.001**				

P1, comparison between control and intervention groups at each time point, McNemar test was used, p2 comparison of repeated measures across time, Freidman's test was used. P3, comparison between both groups across time, mixed linear model was used.

CK-MB showed significantly lower levels in intervention group when compared to control group at 6, 9 and 12 months. Across time points, intervention group showed significant decrease in CKMB levels. Cooling showed statistically significant reduction of CK-MB reduction across time when compared to standard method. Across time points, control group showed no significant difference in CKMB levels (p2>0.05). While, intervention group showed significant decrease in CKMB levels. Cooling showed statistically significant reduction of CK-MB reduction across time when compared to standard method (p3<0.001). (Table 6).

Table (6). Comparison of CK-MB in IU/L among both groups at different follow up points.

	Control group (n = 50)		Intervention group (n = 50)		P^1
	Median	Range	Median	Range	
At baseline	6	5.5-6.9	6.4	5.6-6.9	0.287
After 3 months	5.7	5.6-6.8	5.2	4.8-5.9	0.293
At 6 months	4.8	4.6-6	4.5	4.2-5.5	**<0.001**
At 9 months	5.3	4.2-5.5	4.6	3.9-5	**<0.001**
At 12 months	5.3	4.2-5.5	4.6	4-5.1	**<0.001**
P^2	0.595		**<0.001**		
P^3	**<0.001**				

P1, comparison between control and intervention groups at each time point *Mann-Whitney test and Friedman test* were used, p2 comparison of repeated measures across time. P3, comparison between both groups across time. Post-hoc test was used for multiple p-values.

Overall, there was a significant decrease in Cardiac Troponin-T (cTnT) level across time points in control as well as intervention group (p2<0.001 for each), however, no significant differences were found in troponin level between groups at each time point (p1, p3>0.05 for each) (Table 7).

Table (7). Comparison of Cardiac Troponin-T (cTnT) in ng/ml among both groups at different follow up points.

	Control group (n = 50)		**intervention group (n = 50)**		***P*[1]**
	Median	**Range**	**Median**	**Range**	
At presentation	0.56	0.26-0.86	0.66	0.33-0.99	0.106
After 3 months	0.59	0.25-0.95	0.64	0.31-0.93	0.201
At 6 months	0.60	0.29-0.99	0.61	0.29-0.92	0.534
At 9 months	0.60	0.29-0.99	0.62	0.28-0.92	0.904
At 12 months	0.59	0.29-0.98	0.59	0.28-0.93	0.938
***P*[2]**	**<0.001**		**<0.001**		
***P*[3]**	0.234				

P1, comparison between control and intervention groups at each time point *Mann-Whitney test and Friedman test* were used, p2 comparison of repeated measures across time. P3, comparison between both groups across time. Post-hoc test was used for multiple p-values.

By the 6th, 9th, and 12th months, the intervention group had significantly lower frequency of ischemia compared to the control group. ECG-Ischemic changes increased significantly trough time in the control group, while decreased significantly trough time in intervention group. Cooling showed better effect on ischemia across time when compared to standard method (Table 8).

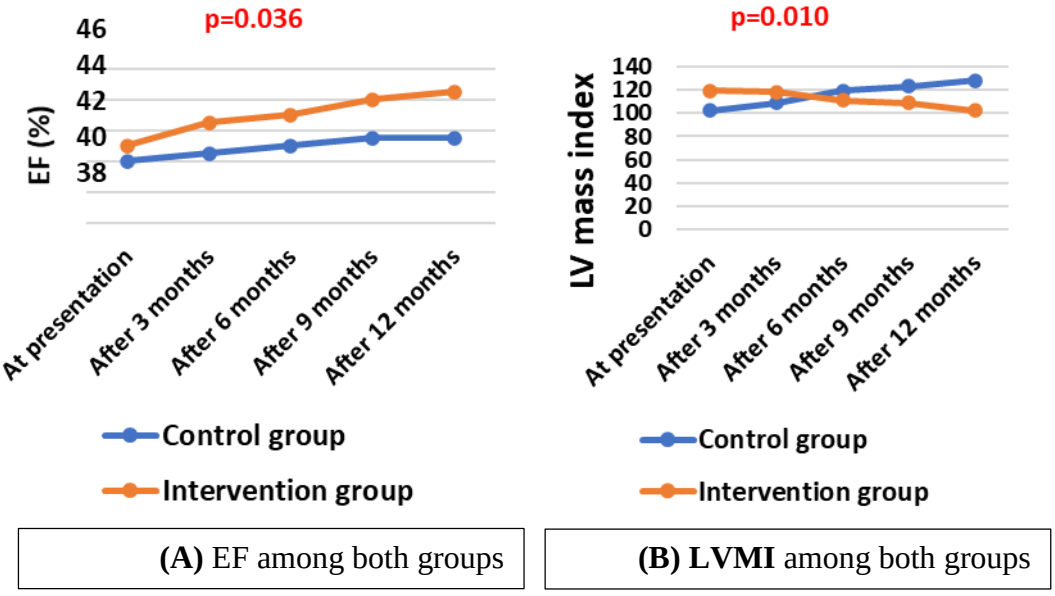
Table (8). Comparison of ECG ischemic findings (ST segment changes, T wave inversion, bundle branch block and pathological Q wave**) among both groups at different follow up points.**

		Control group (n = 50)		**intervention group (n = 50)**		***P*[1]**
		N	**%**	**N**	**%**	
At presentation	**Total**	50		50		
	Ischemia	16	32%	14	28%	0.663
After 3 months	**Total**	50		50		
	Ischemia	20	40%	14	28%	0.205
At 6 months	**Total**	46		46		
	Ischemia	21	45.6%	12	24%	**0.021**
At 9 months	**Total**	46		46		
	Ischemia	20	43.4%	12	26%	**0.038**
At 12 months	**Total**	41		42		
	Ischemia	20	48.7%	11	26.1%	**0.009**
	P2	**<0.001**		**0.001**		
	P3	**<0.001**				

P1, comparison between control and intervention groups at each time point, McNemar test was used, p2 comparison of repeated measures across time, Freidman's test was used. P3, comparison between both groups across time.

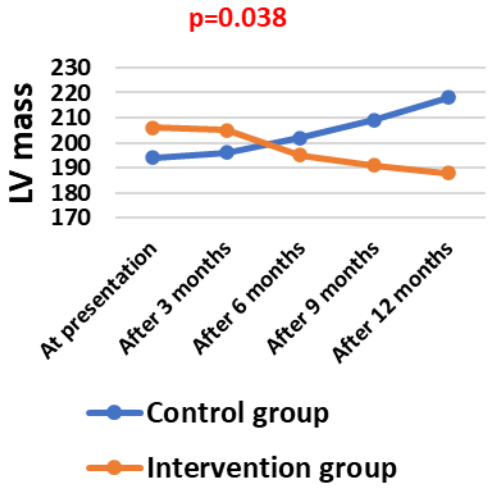
Overall, it is evident from figure (2) that the improvement in EF, LV mass index, LV mass, and LV volume were all statically significantly better in the intervention group compared to the control group**.**

Figure (2). Echocardiographic findings among both studied groups:

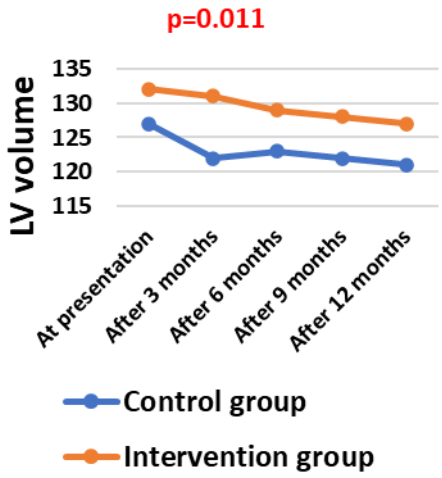


(A) EF among both groups

(B) LVMI among both groups



(C) LV Mass among both groups



(C) LV Volume among both groups

EF: Ejection Fraction, LV: Left Ventricle

(A) EF among both groups at different follow up points.
(B) LVMI among both groups at different follow up points.
(C) LV Maas among both groups at different follow up points.
(D) LV volume among both groups at different follow up points.

There was no statistically significant difference across different time points between groups as regards % of diastolic dysfunction (Figure 3).

Figure (3). **The percentage of Diastolic Dysfunction in the intervention (Group A) vs control (Group B)** showed no statistically significant difference across different time points between groups.

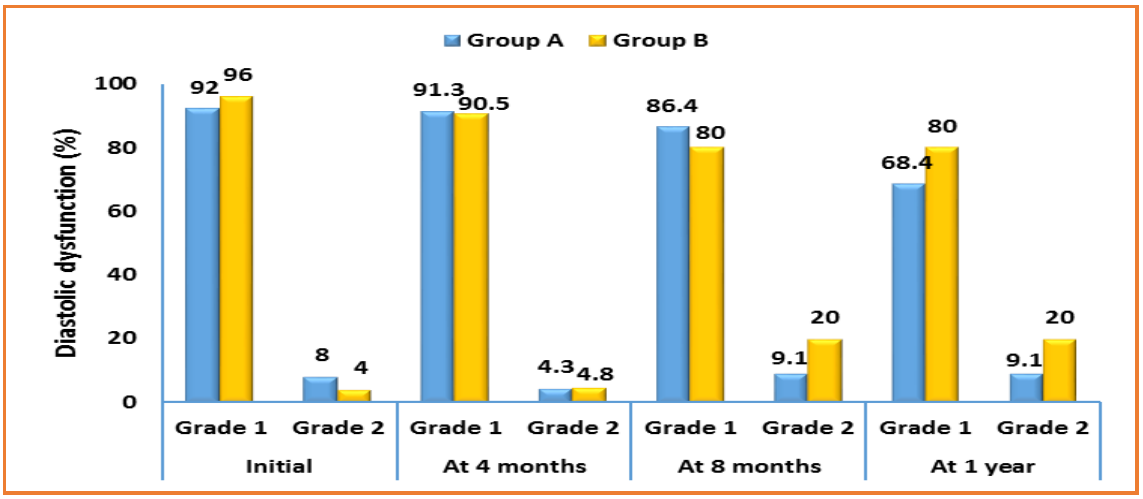


Table (9). Comparison of new myocardial ischemia among both studied groups.

	Control group (n = 50)		intervention group (n = 50)		*P1*
	N	%	N	%	
New Myocardial Ischemia	16	32%	7	14%	**0.032**

P1: **Chi square test was used for comparison**

As shown in table (9), Overall, Intervention group showed significantly lower frequency of new myocardial ischemia (as defined by composite of ECG+ Echocardiographic findings+ CK-MB/Cardiac Troponin-T (cTnT) values) when compared to standard method (p1=0.032),

Cooling was found to be an independent protective predictor against new myocardial ischemia in HD patients using Logistic Regression Analysis (OR 0.54, p-value 0.033, CI: 0.3-0.95) (Table 10).

Table (10). Regression analysis for prediction of new myocardial ischemia in HD patients.

	p	OR	95% CI	
Age	0.202	1.053	0.920	1.088
Gender	0.539	1.190	0.683	2.072
Smoking	0.771	0.909	0.477	1.733
BMI	0.172	1.100	0.959	1.261
Comorbidities	0.392	1.376	0.869	1.849
Hemoglobin (g/dl)	0.089	1.159	0.978	1.374
Albumin(g/dl)	0.140	2.328	0.837	5.226
Cholesterol (mg/dl)	0.277	1.005	0.996	1.015
Dialysate Cooling (CD)	**0.033**	0.542	0.308	0.952

OR, odds ratio; CI, confidence interval, BMI: body mass index.

DISCUSSION

Overall, the intervention group individualized to Cooled Dialysis (CD) showed a significantly lower trend for developing new myocardial ischemia (composite of ECG+ Echocardiographic findings+ CK-MB/Cardiac Troponin-T) when compared to standard temperature group. In the logistic regression analysis performed to account for the interaction with other independent variables, dialysate cooling was found to be an independent protective predictor against new myocardial ischemia in HD patients. The mean achieved dialysate Temperature (td) in the intervention versus the control group was (35.3 ± 0.45 vs 36.5± 0.32°C, respectively). The main observed clinical parameter in patients on CD compared to ST group was a statistically less significant rate of Intradialytic Hypotension (IDH), whilst the remainder of achieved Dialysis prescription parameters did not differ significantly between groups (HD treatment Time, Ultrafiltration Rate, Interdialytic weight gain).

Different cooling modalities have been employed in clinical practice and research settings [(15)], yet in all previous studies dialysate temperature (td) was set at 37°C in the control arm [(12)]**.** Noteworthy, a major difference in our present study is that our control group was prescribed a (td) adjusted to the same degree of baseline (CBT) before each HD session. This individualized (td) can be considered a cooling prescription compared to the "standard" td in other studies, which prescribed 37°C for their control groups. The average prescribed temperature in the ST (Control) group was (36.5 ± 0.32); Thus, by individualizing (td) for the control group, the present study can be viewed as comparison between two cooling strategies rather than a classic standard vs cooled HD in previous studies [(12)]**.**

In the present study, HD patients individualized to CD had a statistically significant decline in their CK-MB values across different time points but Cardiac Troponin- T (cTnT) values did not show a similar trend. It is not clear why there was such a discrepancy between the two cardiac biomarkers in the study cohort; however, it is well acknowledged that the interpretation of the diagnostic and prognostic performance of cardiac biomarkers is rather challenging in the setting of HD [(19-20)].

Regarding ECG changes suggestive of new myocardial ischemia, overall, compared to Standard Dialysis (ST) group, HD patients individualized to CD demonstrated less ischemic changes from the 6th month up to the end of the study period. Previous studies using ECG changes obtained during HD procedure demonstrated intradialytic ischemic changes attributed to IDH during the procedure itself in conventional HD patients [(21-22)].

The most significant changes related to the intervention (CD), were demonstrated in the echocardiographic differences between the two study groups. Overall, across different time points, the intervention group showed higher improvement in Ejection Fraction (EF), and better reduction in LV mass index, LV mass, and LV volume. As shown in previous studies in HD patients, the performance of cardiac

geometrical (mal)adaptations have been found to be a fair prognostic cardiovascular risk factor. By indexing LV wall thickness to cavity size, the LV mass-to-volume ratio can be calculated to assess and categorize LV geometry into either concentric remodeling, concentric hypertrophy, or eccentric hypertrophy. As such, the favorable echocardiographic findings in our study cohort individualized to CD are likely to have a better prognostic outcome [23-25], nevertheless, we did not find a statistically significant difference in the diastolic function between the two study groups.

Previous study by **Odudu *et al.*** [17] has used advanced imaging techniques such as CMR and PET-CT scan; however, the validation of echocardiographic findings in HD patients has been confirmed in previous studies where imaging studies using PET-CT scans have clearly demonstrated a pronounced global and segmental decline of myocardial perfusion by a factor of 30% during HD procedure with IDH, even in the absence of coronary artery disease. In these studies, simultaneous 2D echocardiographic scans conducted pre- and during HD have shown that Regional Wall Motion Abnormalities (RWMA) mirrored the pattern and territory of segmental decreased myocardial perfusion in PET-CT scans, thus validating the use of 2D Echo to scan for decreased myocardial perfusion [23-25].

Furthermore, longitudinal imaging studies have found a significant correlation between both baseline myocardial stunning and RWMA detected by PET-CT scans and the 1-year mortality. A multivariate analysis of these studies showed that age, serum Cardiac Troponin T (cTnT) levels, IDH, and UF volumes were the determinants of noted RWMA [26-29]. In our study, the trend for change in Cardiac Troponin T (cTnT) levels was not significant, however, the trend for CK-MB reduction was statistically significant in the intervention group. In addition, incorporating both biomarkers to ECG and echo in the composite end point was statistically significantly better in the CD group.

In a similar proof-of-concept RCT, **Odudu *et al.*** [17] randomized a cohort of incident HD to either standard or cooled dialysate, and showed a potential for CD to delay myocardial stunning as evidenced by CMR imaging. Whereas in the present study, our cohort were selected from maintenance HD patients (average HD vintage 2.5 $\pm$ 1.2 years) to study the impact of CD on myocardial ischemia as measured by serial estimates of surrogates for myocardial ischemia (ECG, echocardiography and cardiac biomarkers) showed a similar trend.

The underlying mechanism accounting for the noted cardioprotective potential of CD in previous studies is not yet settled and remains to be further elucidated [16-18]. So far, mitigating the IDH with its attending hypoperfusion seems to be the major anti-ischemic mechanism observed with CD [14]. In the present study, patients in the CD group experienced less episodes of IDH in terms of frequency and severity as compared to the ST group.

The imperfections and inadequacies of intermittent conventional HD has been well characterized and aptly described by **Depner** [30] as the "residual syndrome" denoting the "unphysiological" nature of HD as a blood purification therapy that removes, at best, only a small part (~ 20%) of uremic toxins, but also creates its own HD-induced disturbances and ill-effects.

In part, the intermittency of HD coupled with short HD treatment time leads to unphysiological cyclical shifts in volume and solutes, thus challenging the heart with repeated loading-unloading cycles, and repetitive stretching-shortening which both, long term, enhance reverse remodeling of the cardiovascular system [31-32]. This phenomenon can be addressed by increasing HD frequency and allowing longer HD treatment time [31-32]. In our study cohort, the mean achieved HD treatment time was satisfactory in both groups (4.25 $\pm$ 0.25 hour in the intervention vs 4.27 $\pm$ 0.31 in the control groups) with a safe ultrafiltration rate (less than 10 ml/min./kg).

A wealth of studies has suggested that setting dialysate temperature (td) arbitrarily at 37°C is unphysiological, by unwittingly exposing HD patients to passive heating during the procedure with rise in CBT and net energy transfer from Extracorporeal HD circuit to the patient. Indeed, dysregulated CBT in HD patients is a well-recognized phenomenon even off-dialysis, the majority of HD patients have lower CBT [33-34]. Such passive rise in CBT during standard HD at 37°C is postulated to have a detrimental effect on the vascular vasoconstrictive and cardiac inotropic responses set to combat the HD-induced hypovolemia, especially with excessive ultrafiltration over short time beyond the capacity of vascular refilling [34]. Hence, Dialysate Cooling (CD) in its simplest form can be viewed as a "re-purposing" of the thermoregulatory mechanisms in HD patients to prevent systemic hypoperfusion, improve HD tolerance and minimize the repetitive episodes of IDH and IRI.

The current study has important limitations that include:

1- The small number of patients makes it hard to perform subgroup analysis in the study cohort or draw confidant generalizations to other HD cohorts.
2- The short follow up time for 1 year only might not be enough for clinical outcomes to materialize; however, the improvement in the surrogate endpoints suggests a potential for hard endpoints to follow the same trend.
3- The open label design was inevitable due to the continuous need to adjust dialysate temperature.

4- The imaging used in our study included only echocardiography, whereas other studies have used advanced imaging modalities, however, the echo findings were validated in previous studies to correlate and mirror the findings in other imaging modalities like Cardiac Magnetic Resonance (CMR) and PET-CT scans [23-25].

In conclusion, our findings in the present study clearly demonstrate a potential for Cooled Dialysis (CD) to minimize the myocardial ischemia in maintenance HD patients individualized for CD against dialysate temperature set lower than CBT. Dialysate Cooling (CD) is a simple, feasible and cost-free adjustment that can be easily and safely applied to any HD machine. Nevertheless, future larger studies with longer follow up time are warranted to confirm our findings in this vulnerable group of HD patients.

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