

Impact of cooled hemodialysis for preservation of residual kidney function among Egyptian patients

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Background/aim

Emerging evidence on lowering dialysate temperature suggests a cardiorenal protective effect of dialysate cooling (CD) against dialysis-induced ischemia in hemodialysis (HD) patients prone to intradialytic hypotension (IDH). Whether this benefit of CD could be extended to incident HD populations without baseline IDH to preserve residual kidney function (RKF) is unknown.

Patients and methods

One hundred incident HD patients were randomly assigned to receive either incremental CD less than or equal to 36°C (intervention, $N=50$ patients) or standard-temperature (ST) dialysate (control, $N=50$ patients) for 12 months. The primary endpoint was to test the safety and efficacy of CD to preserve RKF.

Results

By the end of 12 months, CD patients showed less decline in estimated glomerular filtration rate compared with standard-temperature patients (6.2 vs. 4.6 ml/min/1.73 m², $P=0.025$); in addition, Cox regression analysis showed that CD was an independent variable for the preservation of RKF ($P=0.044$, hazard ratio: 0.478, confidence interval: 0.23–0.89). CD was well tolerated, with less fatigue and IDH; however, coldness, shivering, and discomfort were significantly higher in the CD group.

Conclusion

In incident HD patients without baseline IDH, cooled dialysis might help preserve RKF with a reasonable safety profile. Further studies are warranted to explore these findings.

Keywords:

cooled dialysis, glomerular filtration rate, intradialytic hypotension, randomized-controlled trial, residual kidney function

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Introduction

In hemodialysis (HD) patients, the survival and health benefits of residual kidney function (RKF) remain quite significant, far in excess of dialysis clearance [1]. Even at glomerular filtration rate (GFR) values as low as 1 ml/min/1.73 m², preserved RKF provides longer survival, higher quality-of-life and better health outcomes [2,3]. Yet, maintaining RKF remains a poorly managed target in the HD population.

In fact, HD, in and of itself, can be counterproductive to the RKF preservation in two ways: first, HD is a cardinal circulatory stressor, especially in patients prone to intradialytic hypotension (IDH) [4]. Repetitive episodes of IDH end in a widespread HD-mediated ischemic organ injury with a subsequent decrease in renal perfusion (DRP) [5–7]. Second, setting the dialysate temperature (td) at a ‘one-size-fits-all,’ ‘standard’ 37°C, unwittingly, exposes HD patients to further hemodynamic compromise [8]. The HD-induced heat gain in patients with low baseline core body temperature (CBT) can cause inappropriate

vasodilatation and impairs appropriate vasoconstrictor reflexes, leading to more IDH [9].

Dialysate cooling (CD), in contrast, improves hemodynamic tolerability to ultrafiltration-induced hypovolemia [10]. Traditionally, CD has been used as a first-line option to offset (IDH) [11–13]. More recently, emerging data from randomized-controlled trials (RCTs) have shown a new potential for CD to delay the HD-induced ischemic organ injury. Evolving evidence supports a protective role of CD against myocardial stunning (MS), brain white matter ischemia and DRP [5–7]. The preservation of renal perfusion is a key determinant for maintenance of RKF.

To our knowledge, no previous study has investigated whether the benefit of CD can be extended to other

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HD patients without IDH to protect renal perfusion. Therefore, the aim of the present study was to investigate whether CD could offer a safe and effective means to preserve RKF in incident HD patients without baseline IDH.

Patients and methods

Patients and study design

From October 2018 to October 2020, we conducted an open-label, prospective, RCT to test whether CD would help preserve RKF in incident HD patients.

One hundred incident HD patients 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 *td* prescription settings. The study was carried out as a parallel RCT; however, crossover was allowed between groups if clinically indicated as per the treating physician. Upon follow-up, seven patients assigned to each original arm crossed over to the opposite study arm. Data analysis was carried out eventually as per original treatment allocation with intention-to-treat analysis at the end of the trial period. The duration of the study for each patient was 12 months.

Ethical approval

The study was carried out in accordance with the principles and regulations of the Helsinki declaration. The study protocol was approved by the Ethical Committee of Benha University on 30/9/2018, with approval number 3515/275. All the participants provided an informed written consent in the Arabic language after a full explanation of the study and the potential hazards and benefits was provided.

Intervention

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

- (1) The intervention arm (50 patients) received CD to less than or equal to 36°C, and with a stepwise decrease in *td* by 0.5°C as long as cooling was tolerated down to 35°C.
- (2) The control arm (50 patients) received standard-temperature (ST) dialysate individualized to the same degree of the patient's CBT measured before the HD session.

Conventional HD was delivered to all patients using Fresenius HD4008 B machines, low-flux poly-sulfone

dialyzers and bicarbonate-based dialysate. Dialysate composition was almost similar between groups. CBT was monitored using a Tympanic membrane Thermometer taken at the beginning of HD and then serially every hour.

End points

The primary endpoint of our study was to test; first, efficacy: to determine the difference in the decrease of RKF (both the rate of decline and the proportion of patients with lost RKF) between groups over a 12-month period. In addition, we carried out multiple regression analysis to assess the interaction between RKF and other independent variables (age, sex, comorbidities, and *td*). Second, safety: adverse events in the two groups were recorded and analyzed.

Endpoint definitions

RKF: we adopted the European Best Practice Guidelines (EBPG) and used the averaged urea and creatinine clearances; in addition, we assessed the patient-reported urine output volume as an additional measure of the RKF. Preserved RKF was defined as greater than or equal to 3 ml/kg/1.73 m² and/or urine volume (UV) greater than or equal to 200 ml/day. IDH was defined as per EBPG [11]. Post-HD fatigue was measured using the fatigue severity scale [14].

Inclusion criteria

Incident HD patients with UV greater than or equal to 200 ml/day and estimated GFR greater than or equal to 3 ml/min/1.73 m² were included in the study.

Exclusion criteria

Patients ≤18 years, patients with UV less than or equal to 200 ml/day, patients with baseline hypotension and uncontrolled hypertension, pregnant patients and patients with failed kidney allografts were excluded from the study.

Statistical analysis

The collected data were coded and entered into a PC using the Statistical package for Social Science (released 2017, IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, New York, USA). Parametric data were presented as mean±SD, nonparametric data as median and range and categorical variables as counts (frequency and percentage). As to the Analytical statistics, the Student *t*-test was used to assess the statistical

significance of the mean values. The Mann–Whitney Test was used to assess the statistical significance of variable medians, Wilcoxon's signed tests were used to compare between the baseline characteristics and χ^2 tests were used for qualitative variables. Repeated measures analysis of variance (for parametric) or Friedman's test (for nonparametric) variables were used for comparison of repeated measures across all time points, with post-hoc Bonferroni test used to perform many t -tests at once. Correlation analysis was carried out to assess the strength of association between two quantitative variables expressed as the correlation coefficient. Linear Regression analysis was carried out for prediction of risk factors. The Kaplan–Meier estimate was used to compare the 1-year cumulative survival of RKF between the two study groups. All P values were two-sided; P values less than 0.05 were considered significant.

Results

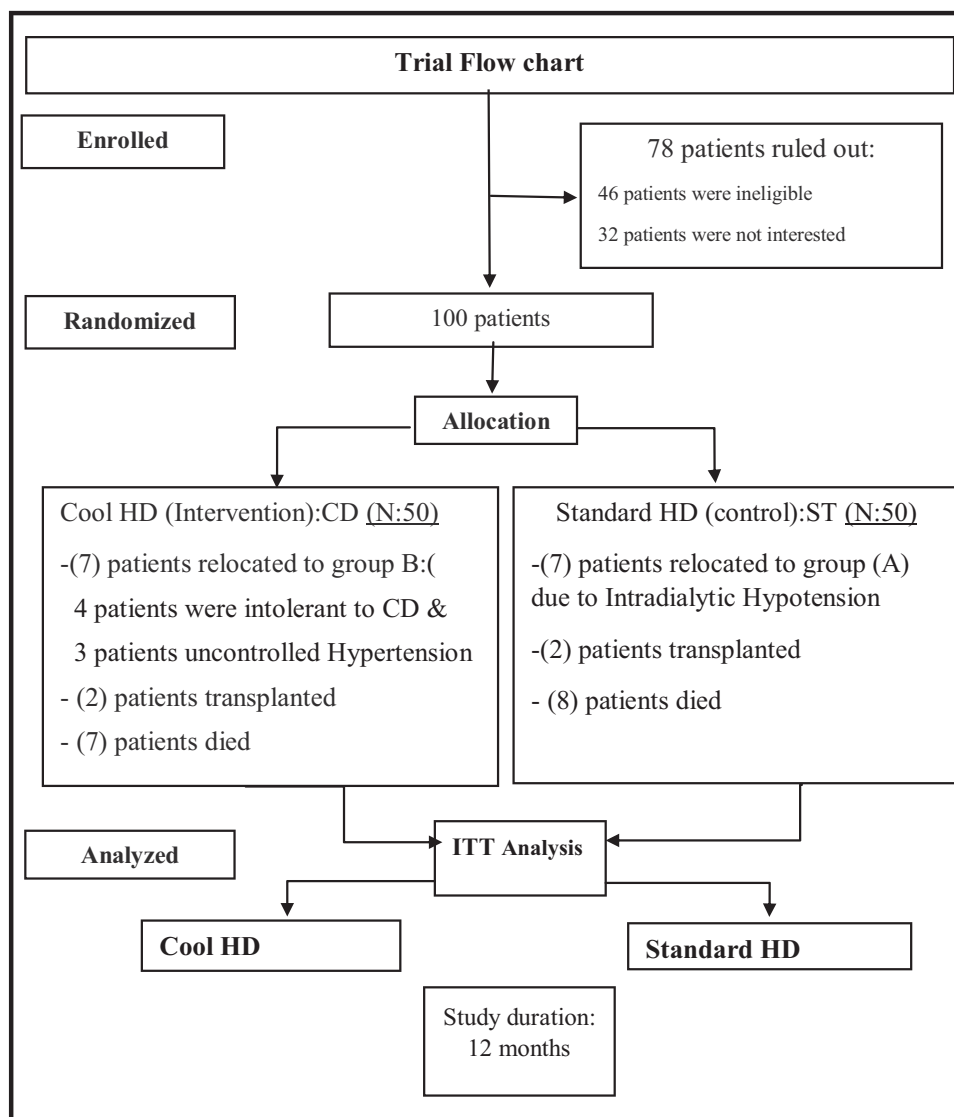
Study population

As shown in Fig. 1, we evaluated 178 incident HD patients for enrollment in the study; 78 patients were ruled out (46 were ineligible and 32 were not interested in the study).

The majority of the study population in both groups were males; otherwise, the baseline characteristics of both randomized groups were balanced, with no significant differences as summarized in Table 1.

With respect to HD prescription, as summarized in Table 2, the average temperature achieved in the CD group was 35.3 ± 0.45 versus 36.5 ± 0.55 in the ST group. The time frequency of sessions, Ultrafiltration (UF)

Figure 1



Trial flow chart as per CONSORT (consolidated reporting of trials).

Table 1 Baseline characteristics of both randomized groups

Characteristics	Cool HD (N=50) [n (%)]	Standard HD (N=50) [n (%)]	P (95% CI)
Age (y)	50.5±15	51±13.9	0.86
Sex: males	34 (68)	38 (76)	0.373
Females	16 (32)	12 (24)	
Body mass index	28.3% (26–34)	27.9% (25.8–33)	0.8
Estimated GFR	9.1±5.3	8.9±5.6	0.85 (–1.96 to 2.36)
Proteinuria	1.2±(0.6–1.8)	1.1±(0.55–1.65)	0.63 (–0.31 to 0.51)
Cause of ESRD			
Diabetes mellitus	17 (34)	16 (32)	>0.05
Hypertension	20 (40)	22 (44)	>0.05
Obstructive uropathy	4 (8)	3 (6)	>0.05
Cystic disease	2 (4)	2 (4)	>0.05
Glomerulonephritis	4 (8)	5 (10)	>0.05
Others	3 (6)	2 (4)	>0.05
Comorbidities			
Heart failure	5 (10)	4 (8)	>0.05
Ischemic heart disease	11 (22)	12 (24)	>0.05
Hepatitis C virus	14 (28)	13 (26)	>0.05
Hepatitis B virus	2 (4)	3 (6)	>0.05
Peripheral vascular disease	6 (12)	7 (14)	>0.05
Stroke	3 (6)	3 (6)	>0.05
Medications			
ACE inhibitors/ARBs	16 (32)	14 (28)	>0.05
Calcium channel blockers	17 (34)	19 (38)	>0.05
Diuretics	12 (24)	13 (26)	>0.05
Beta-blockers	11 (22)	13 (26)	>0.05
Ejection fraction	44.9±5.4	45.3±5.1	>0.05
Blood pressure			
Systolic blood pressure	139±12.4	138±13.2	0.79 (–6.46 to 8.46)
Diastolic blood pressure	85±6.6	85±6.7	0.46 (–1.6 to 3.6)
Mean arterial pressure	103±3.4	102.6±3.86	0.16 (–0.43 to 2.43)

Descriptive statistics: parametric numerical data presented as mean±SD, median and range for nonparametric numerical data. Categorical variables are presented as counts (frequency & percentage). ACE, angiotensinogen converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; ESRD, end stage renal disease; HD, hemodialysis; GFR, glomerular filtration rate.

Table 2 Summary of hemodialysis prescription

Characteristic	COOL HD	Standard HD	P (95% CI)
HD prescription			
Time on HD time (h±min)	3.5±40.2	3.6±41.96	0.30 (–0.29 to 0.09)
HD frequency/year	136.8±4.2	138.2±5.9	0.17 (–3.4 to 0.6)
Rate of UF (ml/kg/h)	8.5±4.2	8.7±4.9	0.82 (–2.0 to 1.6)
Amount of fluid removed	2.1±0.56	2.2±0.51	0.35 (–0.3 to 0.1)
IDWG (intradialytic weight gain)	2.35±1.2	2.41±1.16	0.79 (–0.52 to 0.40)
The achieved dialysate temperature (mean)	35.3±0.45	36.5±0.55	0.0001 (–2.0 to –1.6)
Urea removal rate targets (% of sessions)	80.26±4.5%	79.82±4.7%	0.18 (0.7 to 3.3)

Parametric numerical data as mean±SD, and median and range for nonparametric numerical data. CI, confidence interval; HD, hemodialysis; IDWG, intra-dialytic weight gain; UF, ultrafiltration.

rates, and achieved URR targets were, overall, similar between groups.

As to adverse events as shown in Table 3, the rate of coldness, shivering and discomfort was significantly higher in the cool HD group ($P>0.005$); nevertheless, most of the patients (96%) were able to tolerate most of the prescribed sessions (96.4%). Furthermore, the CD group reported less fatigue after HD.

Blood pressure values were higher in the DC group compared with the ST group as shown in Table 3; in addition, patients in the DC group needed more blood pressure medications compared with the standard group (average 0.25 more tablets), whereas IDH rates were higher in the ST (14%) versus CD group (6%) for the same UF rate and liters removed/session. As per the treating physician, seven patients were switched from CD to standard HD (four due to cold dialysate

Table 3 Adverse events in the study groups (cooled vs. standard hemodialysis group)

Characteristic	COOL HD	Standard HD	P (95% CI)
Symptoms during HD			
Coldness	65.6±2.3%	6.8±1.6%	0.0001
Shivering	18%	2%	0.001
Discomfort	20±1.4%	8±1.4%	0.001
Fatigue after HD	31.34±11.6%	54±1.9%	0.001
Blood pressure (average readings)			
SBP (predialysis)	145±11.4	141±10.9	0.076 (−0.4 to 8.4)
DPB (predialysis)	89±5.9	87±4.8	0.066 (−0.13 to 4.1)
MAP (predialysis)	107±2.19	105±2.3	0.001 (1.1 to 2.8)
Number of blood pressure pills	2.4±1.2	2.1±1.1	0.19 (−0.15 to 0.75)
Diuretics in the last 6 months	58% of patients	34% of patients	0.0001
Intradialytic hypotension (IDH)	6%	14%	0.001
CVC (central venous catheter)	54%	56%	>0.05
% Thrombosis	12%	12.4%	>0.05
AVF (arteriovenous fistula)	42%	41%	>0.05
% Thrombosis	5.9%	6.1%	>0.05
AVG (arteriovenous graft)	4%	3%	>0.05
% Thrombosis	0	0	>0.05
ACS (acute coronary syndrome)	12%	11.8%	>0.05
CVS (cerebrovascular stroke)	3%	4%	>0.05
Death	(7 patients) 14%	(8 patients) 16%	>0.05

CI, confidence interval; DBP, diastolic blood pressure; HD, hemodialysis; SBP, systolic blood pressure.

Table 4 Differences in residual kidney functions between the two study groups

Characteristic	Median	Cool HD	Standard HD	P
Median residual kidney function (eGFR) (ml/min/1.73 m ²)				P ₁
First month	Median	9.7 (5.6–14.8)	9.6 (5.7–14.6)	0.12
Fourth month	Median	8.4±2.9	7.1±2.78	0.059
Eighth month	Median	6.8±2.34	4.9±2.78	0.032
12th month	Median	6.2±1.89	4.6±1.74	0.043
	P ₂	<0.001	<0.001	0.025
	Post-hoc test	P ₃ <0.001	P ₃ <0.001	
		P ₄ <0.001	P ₄ <0.001	
		P ₅ <0.001	P ₅ =0.116	

The CD group showed significant preservation of RKF compared with the ST group across different time points. CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; P₁, comparison between cool and standard HD groups during each 4-month duration using the Mann–Whitney U-test; P₂, comparison of repeated measures across all time points, using Friedman's test; P₃, comparison between the initial and the fourth month; P₄, comparison between the fourth and the eighth month; P₅, between the eighth and the 12th month.

intolerance and three for high blood pressure). In contrast, seven patients were transferred from the standard group to the CD group due to IDH. There was no significant difference in the deaths in the CD group versus the ST group (seven vs. eight, respectively). Death was due to sepsis (3,2), arrhythmia (2,2), Heart Failure (HF) (1,2), and liver disease (1,2), respectively.

End points

As shown in Table 4, cool HD was more effective in preserving the RKF as evidenced by the slower rate of eGFR decline that was statistically significant in the cool HD group (using the Friedman test for comparison of repeated measures across time; $P=0.025$). In addition, as shown in Table 5, the percentage of patients who had a preserved eGFR was also higher in the cool HD group.

Using the Kaplan–Meier survival analysis, 64.2% of the patients survived without loss of RKF, mean time 10.2 months, while in the standard HD group, only 43.7% survived without loss of renal function, mean time 8.4 months.

As shown in Table 6, Cox regression analysis carried out to adjust for covariates revealed that cool HD was an independent variable for the preservation of RKF after adjustment of the other variables ($P=0.044$, hazard ratio: 0.478, confidence interval: 0.23–0.89).

Discussion

Among (100) incident HD patients randomized to either cooled dialysis (CD) or standard (ST) td, we

Table 5 Percentage of patients with residual kidney functions in each study group

Characteristic	CD group	ST group	P
Month			
Preserved RKF%	Preserved RKF%	Preserved RKF%	P_1 value
First month			
Preserved RKF%	100%	100%	–
Censored	0	0	–
Died	0	0	–
Fourth Month			
Preserved RKF%	84%	72%	0.509
Censored	6	4	–
Died	2	2	–
Eighth month			
Preserved RKF%	72%	54%	0.018
Censored	1	2	–
Died	2	4	–
12th month			
Preserved RKF%	66%	40%	0.018
Censored	2	3	–
Died	3	2	–
Total (censored)	9 (2 Tx)	9 (2 Tx)	–
Total (died)	7	8	–
P_2	<0.001	<0.001	
Post-hoc test	$P_3=0.125$	$P_3=0.013$	
	$P_4=0.016$	$P_4<0.001$	

One- way repeated measures analysis of variance: the % of patients with preserved RKF was statistically higher in the CD group. The F -ratio value is 8.15686. The P -value is 0.046. CD, dialysate cooling; P_1 , comparison between CD and ST groups during each 4-month duration using the Mann–Whitney U -test (0.5, 0.018, 0.18); P_2 , comparison of repeated measures across all time points using Friedman's test; P_3 , comparison between the initial and the fourth month; P_4 , comparison between the fourth, eighth, and 12th month; RKF, residual kidney function; ST, standard-temperature.

Table 6 Cox regression analysis for prediction of shorter time of loss of renal function

Characteristic	P	HR (hazard ratio)	95% CI (confidence interval)	
Age	0.54	1.007	0.985	1.03
Sex (male)	0.27	0.96	0.314	1.384
Hypertension	0.16	1.806	0.786	4.151
Diabetes mellitus	0.19	1.23	0.81	1.7
Cooling dialysate	0.044	0.478	0.233	0.981

Statistically significant.

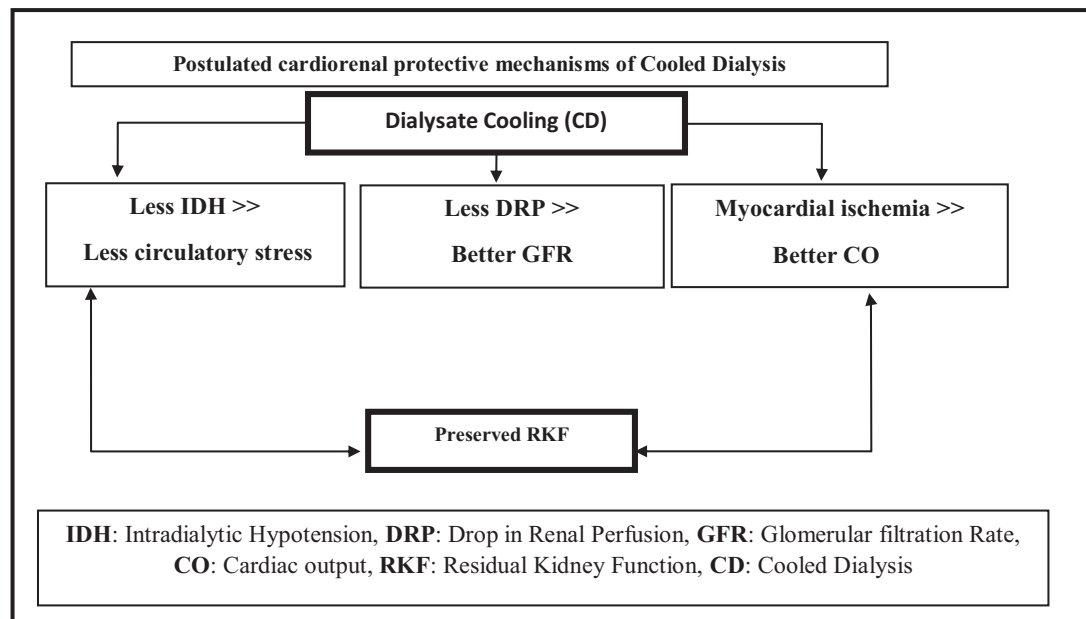
found that by the end of 12 months, the CD group showed less decline in eGFR. In addition, more patients in the CD group had preserved RKF compared with the ST group. The mean time of 1-year cumulative survival without loss of RKF on Kaplan–Meier analysis was 10.8 months in the CD group versus 8.4 months in the ST group. Cox regression analysis carried out to adjust for age, sex, and comorbidities revealed that cool HD was an independent variable for the preservation of RKF after adjustment of the other variables.

The marginal difference in RKF noted between the CD and ST groups at the end of the study is likely to be

clinically significant; previous studies have shown that minimal amounts of preserved eGFR as low as 1 ml/min/1.73 m² lead to survival and health benefits [1–3].

The present study is the first to use CD for preservation of RKF in incident HD patients. The rationale for performing this RCT derives from previous studies showing a cardiorenal risk reduction in patients individualized to CD, by delaying the ultrastructural ischemic organ injury accruing during repetitive episodes of the hypoperfusion caused by IDH [5–7]. McIntyre and coworkers have shown HD to inversely cause a contemporary DRP and MS, even without significant hypotension, and have demonstrated that CD minimized DRP and MS, albeit not statistically significant [5]. Conversely, in the present study, patients individualized to CD achieved a statistically significant higher preserved RKF. It should be noted that McIntyre's cohort of patients included vintage HD patients (5.3 years on HD) with low RKF and received CD for 1 session only, whereas in our study, incident HD patients with higher RKF received CD for 1 year. The underlying mechanisms accounting for this protective role of CD are still elusive and at best speculative [10]. We

Figure 2



Postulated cardiorenal protective mechanisms of cooled dialysis to preserve residual kidney functions.

hypothesized that CD by its cardiorenal protective effect would help preserve RKF by maintaining renal perfusion and minimizing myocardial injury and circulatory stress (as depicted in Fig. 2).

Different cooling modalities have been used [15]; yet, in all previous studies, the *td* was set to 37°C in the control arm [13]. Abundant evidence [16,17] suggests that the so-called ‘standard’ *td* arbitrarily set to 37°C is unphysiological, in the sense that it inadvertently exposes patients to supraphysiological heating during HD with net energy transfer to the patients. The impact of this increase in CBT during HD can be quite detrimental because it offsets the thermal autoregulatory mechanisms set to combat IDH [16]. Thus, a cardinal difference that sets our present study apart from previous work is that our control group was prescribed a (*td*) adjusted to the same degree of baseline (CBT) before each HD session. This individualized iso-thermic (*td*) is a cooling prescription compared with the ‘standard’ *td* in other studies that prescribed 37°C for their control groups. The average prescribed temperature in the ST (control) group was 36.5±0.55. Thus, by individualizing (*td*) for the control group, the present study can be viewed as more of a comparison between two cooling strategies rather than a classic standard versus cooled HD in previous studies [13].

The cohort population in our study has a male predominance; Apart from sex, the rest of the cohort demographics were similar. Nevertheless, it should be noted that our population is different

from previous studies on CD in two fundamental aspects: first, they are incident HD patients with short HD vintage (<1 month) and higher baseline RKF (9.7 and 9.6 min/ml/1.72 m², respectively). Previous studies enrolled patients with long HD vintage [5,13]; however, an earlier study [18] suggested that early IDH during the first 3 months negatively affects RKF, and hence, individualizing incident HD patients to CD early on is more beneficial. Second, in the present study, baseline IDH was an exclusion criterion. Previous studies have addressed the benefits of CD to ameliorate IDH [10]; while those studies were quite justified and plausible, it should be noted that IDH itself might be a confounder for a higher comorbidity index (an epiphenomenon) [19]. In addition, patients with frequent IDH require other interventions such as sequential ultrafiltration, sodium profiling, volume expanders and vasopressors. Such interventions are likely to confound the impact of CD on RKF.

With respect to safety, coldness-related symptoms were, as expected, significantly higher ($P>0.005$) in the CD group; nevertheless, most of the sessions were tolerated in most of the patients in the CD group. It is noteworthy that IDH and fatigue were significantly less in the CD group. Still, in our cohort, IDH occurred in 6 versus 14%, respectively, despite (*td*) individualization. The occurrence of IDH speaks to the complexity of IDH and the multitude of factors driving it.

The observed higher BP values in the CD are likely directly related, at least in part, to CD itself. Given the fact that for the same degree of UFR, patients on CD had higher BP values and needed higher doses of BP medications, it is noteworthy that data on high BP effect on RKF are not consistent [20,21] and are mostly derived from patients on peritoneal dialysis.

It is fair to acknowledge that our study has some salient limitations including the following:

- (1) Small number of patients; however, incident HD patients are difficult to recruit in large numbers from a single center.
- (2) No imaging of the renal perfusion was performed; using a contrast material in our cohort would have negatively affected the RKF.
- (3) In the present study, we used averaged urea and creatinine clearance and urine volume as surrogate markers for RKF. Notwithstanding their imperfections and limitations of performance [22], there is no universal consensus on the ideal markers to assess RKF [23].
- (4) Open-label design: Blinding (of the intervention) was not technically feasible.
- (5) Conventional HD was prescribed to all participants; how much (HDF, ultrapure dialysate) would contribute to the RKF preservation remains to be answered in future studies.

The findings of the current study demonstrate that cooled dialysis can be safely advocated to preserve RKF in incident HD patients. This might have even further implications if data are confirmed in other settings where renal recovery is a crucial target, as in patients with acute kidney injury.

Conclusion

Taken together, our findings demonstrate that cooled dialysis is a safe modality in incident HD patients that can be used to preserve RKF. CD is a simple, cost-free and feasible adjustment that fits well into the current model of HD care. Nevertheless, these findings should be interpreted with great caution. This study is hypothesis generating/proof of concept, suggesting that individualization is key. Given the benefits of CD in the vulnerable HD population, further future studies are warranted to confirm the findings of this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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