ORIGINAL ARTICLE

Effect of Different Dialysate Temperatures on Beta-2-Microglobulin Reduction in Hemodialysis Patients

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Background: Higher body temperature can induce systemic vasodilation and decrease inter-compartmental resistance, a major barrier of middle-molecule toxin clearance in hemodialysis (HD).

Objective: To determine the effect of high dialysate temperature which increases body temperature on Beta-2-Microglobulin (B2M) reduction.

Materials and Methods: A cross over randomized control trial was conducted in stable HD patients between October and December 2017. Subjects were randomized into 2 sequences: (A) dialysis with 35°C then 37°C dialysate, and (B) dialysis with 37°C then 35°C dialysate. Each dialysis period lasted for 2 weeks and was washed out by dialysis with 36°C dialysate. Primary outcome was mean difference of B2M percent reduction ratio (%RR) determined by using pair t-test.

Results: Total 27 HD patients with mean age of 65.9±8.8 years and blood pressure (BP) 158/66 mmHg were enrolled. In sequence A, pre-dialysis B2M levels of 35°C and 37°C dialysates were 27.7±14.6 mg/dL and 26.2±5.9 mg/dL, and post-dialysis levels were 8.7±5.6 mg/dL and 7.2±2.6 mg/dL. In sequence B, pre-dialysis B2M level of 37°C and 35°C dialysates were 27.1±3.6 mg/dL and 24.9±7.6 mg/dL, post-dialysis levels were 6.4±2.7 mg/dL and 9.0±3.4 mg/dL. Overall treatment effect on B2M %RR was higher in the 37°C dialysate (mean difference -9.7±10.3%, 95% confidence interval -15.9 to -3.5, p=0.03). No significant difference in %RRs of blood urea nitrogen, creatinine, and electrolytes among the two temperatures. The difference of mean arterial BP was lower in the 37°C dialysate group (-4.3±2.83 mmHg, p<0.01). No major adverse events were noted in either group.

Conclusion: Raising of dialysate temperature to 37°C increased B2M reduction and slightly decrease in mean arterial BP compared with 35°C dialysate. Therefore, warm dialysate may be considered for enhanced reduction of B2M in stable HD patients with moderately high BP. However, long-term clinical outcomes with using 37°C dialysate need to be confirmed.

Keywords: Hemodialysis; Dialysate temperature; Inter-compartmental resistance; Beta-2-Microglobulin (B2M) clearance; Reduction ratio

Received 9 April 2024 | Revised 10 July 2024 | Accepted 2 August 2024

J Med Assoc Thai 2024;107(Suppl. 1):S118-25

Website: http://www.jmatonline.com

Beta-2-Microglobulin (B2M), a representative marker of middle-molecule uremic toxin, is progressively accumulated in renal dysfunction especially in end-stage kidney disease (ESKD) and high B2M levels relate with mortality, cardiovascular disease, amyloidosis, and inflammation[1-4]. In HEMO study, Patients with B2M levels of 42.5 to 50 mg/L had relative risk of death that were approximately 60% greater than those with B2M levels <27.5 mg/L[5]. Conventional hemodialysis (HD) with low-flux or high-flux dialyzer effectively removes small uremic toxins like urea, however, lesser eliminates B2M due to its larger size. The Newer HD technique (convective-dependent hemodialfiltration; HDF), and larger-pore membrane (medium-cutoff and high-cutoff dialyzers) have been developed to better improve the B2M clearance. Another barrier of B2M removal is intercompartmental resistance which means the difficulty of B2M molecules face when moving between the body compartments into circulation[6,7]. Main factors affect this resistance are size and shape of the molecule which larger molecules, like

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How to cite this article:

Phisutrattanaporn J, Kongpetch S, Tachaiya R, Jansorn S, Wiangnon P, Pongsutat P, Sirirat Anutrakulchai S. Effect of Different Dialysate Temperatures on Beta-2-Microglobulin Reduction in Hemodialysis Patients. J Med Assoc Thai 2024;107(Suppl.1):S118-25

DOI: 10.35755/jmedassocthai.2024.S01.S118-S125

B2M, generally encounter more resistance than smaller ones, and magnitude of blood flow that insufficient blood flow to a compartment can limit the movement of molecules in and out[6,8,9]. Increases of time and frequency of dialysis are the procedures that enhance the intercompartmental mass transfer and further decrease of plasma B2M levels[6]. In addition to these approaches, Maheshwari V. et al. have postulated a rationale and suggested a study design for dialysate temperature manipulation that may impact uremic toxins removal[10].

In general, the standard practice for maintenance hemodialysis involves using a dialysate temperature of 36.5°C or 37.0°C[11,12] while cooler dialysate (≤36°C) or personalized cooler dialysate, i.e., dialysate temperature is 0.5 to 0.9°C below pre-dialysis body temperature, with a minimum dialysate temperature of 35.5°C, is applied in some HD centers[12]. Usage of warm dialysate may increase mobilization and removal of toxins due to elevated body core temperature which augments vasodilation, reduces peripheral resistance, enhances cardiac output and inter-compartmental mass transfer, and reduces post-dialysis rebound of toxins[10]. In the other hand, although cool dialysate can prevent intradialytic hypotension, the resulting vasoconstriction may interfere with the transfer and elimination of toxins from body compartments into vascular compartment[8,10].

Previous studies reported the neutral effects of cool dialysate on urea clearance[13]. Although percent reduction ratios (%RR) of B2M by high-flux dialyzers were reported in range of 59.2 to 74.6%[14-16], however, there is no any study that explores the effect of dialysate temperature on B2M reduction. The purpose of the present study was to prove the hypothesis that high dialysate temperature whether increase solute reduction especially the middle molecule toxin compared with the cool dialysate. Furthermore, adverse events of this dialysate temperature manipulation were determined.

Materials and Methods

Study design and population

The cross over randomized control trial was conducted at renal center of the Srinagarind Hospital, Khon Kaen University between October 2017 and December 2017. All ESKD patients on conventional high-flux HD in the hemodialysis unit were screened. The stable HD subjects who met the inclusion criteria: age ranged 18 to 70 years, undergoing HD three times a week with dialysis vintage ≥3 months, and willing to cooperate in the present study were recruited. Patients were excluded if they had severe hypertension (systolic blood pressure; SBP >180 mmHg and/or diastolic blood pressure; DBP >115 mmHg) or severe hypotension (SBP <100 mmHg and/or DBP <60 mmHg[10], intradialytic hyper- or hypotension within the last 3 months, recent stroke or myocardial infarction or unstable angina within the past 6 months, significant valvular disease or arrhythmia (atrial fibrillation, ventricular tachycardia), and ejection fraction <40% by echocardiogram.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki that was approved by the Ethics Committee for Human Research, Faculty of Medicine, Khon Kaen University, Thailand (project number HE601235 and HE671146). All patients were provided written informed consents.

Processes of randomization and intervention (Figure 1)

Eligible patients were randomly assigned in a 1: 1 ratio using the table of random number method. All recruited subjects underwent the two alternated study sequences: (A) dialysis with 35°C then 37°C dialysate, and (B) dialysis with 37°C then 35°C dialysate with each dialysis period lasted for 2 weeks. To avoid any carry over effect from the previous study period, HD with 36°C dialysate temperature for 2 weeks before alternation to the other dialysate temperature (i.e., wash out period) was conducted. Therefore, all patients were exposed to the 3 dialysate temperatures (35 vs. 37°C, 36°C, and 37 vs. 35°C). All HD sessions were performed with Fresenius 4008S machines, HD duration for 4 hours, usage of reused high flux dialyzers [polysulfone, REXEED-A® with sieving coefficient of B2M 0.8 and ultrafiltration coefficient (Kuf) 81 ml/hr/mmHg (surface area 1.8 m^2) and 90 ml/hr/mmHg (surface area 2.1 m^2)], detected access recirculation occurring <10%, blood flow rate 300 mL/min and dialysate flow rate 500 ml/min. Besides the dialysate temperature, other HD prescriptions, dialysis schedule, and related medications (e.g., phosphate binder, antihypertensive and hypoglycemic drugs, erythropoietic stimulating agents) remained unchanged.

Data and samples collection

Baseline characteristics and demographic data, e.g.,

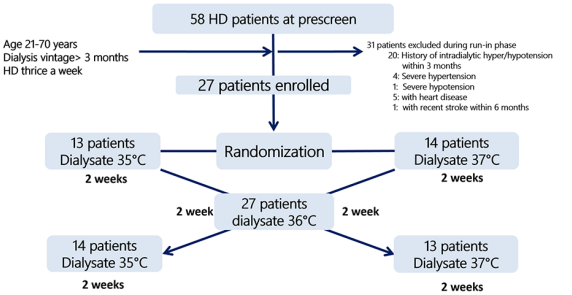

Figure 1. Schematic flow diagram of clinical study.
HD=hemodialysis

age, sex, comorbid diseases, current medications, date of dialysis initiation, volume status, and HD prescriptions were reviewed and collected from interviews, physical examination, and medical records.

During the study intervention, routine HD records were collected including dialysis prescription, pre- and post HD weights, ultrafiltration volume, all intradialytic complications including uncomfortable feeling, and online Kt/V monitoring. The vital signs were monitored throughout the dialysis session, measured every 30 minutes from initiation till the end of HD. Intradialytic hypertension was defined as mean arterial pressure (MAP) increased >15 mmHg within or immediately post dialysis[13], and intradialytic hypotension was established if decreased in SBP ≥20 mmHg or MAP ≥10 mmHg with associated symptom or requiring for treatment[17].

Pre- and post-dialysis blood samples were collected at the last HD session of the two-weeks period with the same operated nurse and technique (i.e., stop dialysate pump technique). 8 ml of blood samples were stored and divided into 2 tubes, i.e., 3 ml in EDTA tube for complete blood count, and 5 ml in clot blood tube for blood chemistry examination. All samples were analyzed in the central laboratory of Srinagarind Hospital for urea, creatinine, electrolytes, B2M, complete blood count and blood sugar. The pre- and post-dialysis blood samples were used to calculate the percent reduction ratio (%RR) of toxins which equals 100 multiplied with difference of pre-concentration and post- concentration divided by pre-concentration.

Definition of exposures and outcomes

Differences in %RR of solutes between the two different dialysate temperatures (35° C and 37° C) were determined which different %RR of B2M was primary outcome, whereas secondary outcomes included 1) the different %RRs of blood urea nitrogen (BUN), creatinine, electrolytes, and blood sugar 2) comparison of vital signs (blood pressure, pulse rate, body temperature, respiration rate), online Kt/V and ultrafiltration volume during each hemodialysis session between the two dialysate temperature sequences.

Statistical analysis

Sample size was calculated by using a 2×2 cross-over design in which the outcome is a continuous normal random variable referenced from Chow SC, et al.[18]. Because there is no reported data of serum B2M reduction in different dialysate temperatures, we speculated the clinical meaningful of B2M reduction as the reported difference of %RR between usage of high-flux and super-flux dialyzers on B2M clearance at week 2 with the mean difference of 6.85 %, a standard deviation of 10.01%[19], and superiority margin of 5.5%. At least 24 subjects would be recruited for the desired level of statistical significance at 0.05 and the 90% power.

Continuous data were expressed as mean ± standard deviation (SD) or median and 25th to 75th percentile (interquartile range, IQR). Categorical data were expressed as number and percent of total participants. The primary outcome between the two groups were evaluated three effects of carry over, period and sequence, occurring in a cross over design and determined the significance of mean difference by using pair t-test. Comparisons of continuous variables among the two groups were used pair t-test or Mann-Whitney U test and expressed as mean or median different and 95% confident interval (CI). Chi-square test or Fisher's exact test was used for comparison of categorical variables. Statistical analysis was done by using STATA version 17 and p-value <0.05 was considered as statistical significance.

Results

Baseline characteristics

Between Octobers 2017 and December 2017, a total of 58 patients were screened, of whom 27 underwent randomization. 31 patients were excluded during run-in phase (i.e., 20 patients of intradialytic hyper/hypotension

Table 1. Baseline characteristics of the participants

Baseline characteristics	Participants (n=27)
Age (year), mean ± SD	65.9±8.8
Women (n, %)	9 (34)
AVF (n, %)	26 (96)
Height (CM), mean ± SD	162.1±6.9
Dry weight (kg), mean ± SD	60.3±11.2
BMI (kg/m^2), mean ± SD	22.9±3.4
Dialysis vintage (year), mean ± SD	5.4±3.5
Mean SBP (mmHg), mean ± SD	158.1±0.2
Mean DBP (mmHg), mean ± SD	66.4±1.4
DM (n, %)	16 (59)
HT (n, %)	27 (100)
DLP (n, %)	24 (88)
IHD (n, %)	8 (30)
Recent stroke (n, %)	3 (11)
Anemia in CKD (n, %)	22 (73)
Hyperparathyroidism (n, %)	5 (18)
Adrenal insufficiency (n, %)	1 (3)

AVF=arteriovenous fistula; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; DM=diabetes mellitus; HT=hypertension; DLP=dyslipidemia; IHD=ischemic heart disease; CKD=chronic kidney disease; SD=standard deviation; n=number

Anemia in CKD defined as hemoglobin <12 g/dl in men and <11 g/dl in women[20]; Hyperparathyroidism defined as intact PTH levels >9 times of the upper normal limit for the assay[21].

within 3 months, 4 patients of severe hypertension, 1 patient of severe hypotension, 5 patients of severe heart diseases and 1 patient of recent stroke within the past 6 months). Overall baseline characteristics as shown in Table 1 were mean age 65.9±8.8 years, female of 34%, mean SBP 158.1±0.2 mmHg, mean DBP 66.4±1.4 mmHg and mean dialysis vintage 5.4±3.5 years. All participants had companying hypertension and 56 % of them had diabetes.

Primary outcome (Table 2)

In sequence A (patents exposed to 35°C dialysate first), mean pre- and post-dialysis B2M levels in 35°C dialysate group were 27.7±14.6 mg/dL and 8.7±5.6 mg/dL, mean pre- and post-dialysis B2M levels in 37°C dialysate group were 26.2±5.9 mg/dL and 7.2±2.6 mg/dL. %RR of both groups was 65.7±18.1% and 72.6±9.1%, mean difference of %RR was -6.9±19.5%, p=0.23.

In sequence B (patents exposed to 37°C dialysate first), mean pre- and post-dialysis B2M levels in 37°C dialysate group were 27.1±3.6 mg/dL and 6.4±2.6 mg/dL, mean pre- and post- dialysis B2M levels in 35°C dialysate group were 24.9±7.6 mg/dL and 9.0±3.4 mg/dL. %RR of both groups was 75.8±10.5% and 63.7±9.3%, mean difference of %RR was 12.1±13.5%, p=0.005.

After adjustment of the carry over, period, and sequence effects of the cross over design, overall treatment effect between both dialysate temperature groups demonstrated the significant difference in %RR by the 37°C dialysate group had more reduction than in the 35°C dialysate group (%RR of B2M 74.2±9.8% vs. 64.7±14.0%) with the mean difference of -9.7±10.3% (95% CI: -15.9 to -3.5, p=0.03). All the three effects analyses revealed that dialysate temperature in each session were independent from others [carry over effect 2.8±13.5 (95% CI: -5.3 to 11.0, p=0.68), period effect -1.06±14.2 (95% CI: -9.7 to 7.5, p=0.85) and sequence effect (p=0.85)]. In addition, the %RR of B2M significantly enhanced with increasing of dialysate temperatures, i.e., 64.7±14.0, 66.7±7.6, and 74.2±9.8 in 35°C, 36°C and 37°C dialysate temperatures groups, respectively (p=0.005).

Secondary outcomes

No significantly different %RR of small molecule toxins, e.g., BUN, creatinine, serum sodium, potassium, phosphate, and calcium in both dialysate temperature groups (Table 3).

Intradialytic monitoring

During each session of HD, vital sign, ultrafiltration

Table 2. Treatment effects of different dialysate temperatures on Beta-2-Microglobulin reduction

Treatment sequence	Treatment period		Within individual difference	p-value
	Initial	Final		
Sequence A; 35 then 37°C				
Mean pre-dialysis B2M (mg/dL), mean±SD	27.7±14.6	26.2±5.9		
Mean post-dialysis B2M (mg/dL), mean±SD	8.7±5.6	7.2±2.6		
Mean percent reduction (%), mean±SD	65.7±18.1	72.6±9.1	-6.9±19.5	0.23
Sample size	13	13		
Sequence B; 37 then 35°C				
Mean pre-dialysis B2M (mg/dL), mean±SD	27.1±3.6	24.9±7.6		
Mean post-dialysis B2M (mg/dL), mean±SD	6.4±2.6	9.0±3.4		
Mean percent reduction (%), mean±SD	75.8±10.5	63.7±9.3	12.1±13.5	<0.01
Sample size	14	14		
Treatment effect				
Percent reduction difference (%), mean±SD			-9.7±10.3	0.03
95% CI			(-15.9 to -3.5)	
Carry over effect				
Percent reduction difference (%), mean±SD			2.8±13.5	0.68
95% CI			(-5.3 to 11.0)	
Period effect				
Percent reduction difference (%), mean±SD			-1.1±14.2	0.85
95% CI			(-9.7 to 7.5)	
Sequence effect				
Percent reduction difference (%), mean±SE			-0.7±3.5	0.86
95% CI			(-7.8 to 6.5)	

B2M=Beta-2-Microglobulin; SD=standard deviation; SE=standard error; CI=confidence interval

Table 3. Percent reduction ratio of small-molecule uremic toxins and electrolyte between the two dialysate temperature groups

	% Reduction ratio 35°C group	% Reduction ratio 37°C group	Mean difference of % Reduction ratio	p-value
BUN	77.4±6.7	71.8±16.3	-5.6±6.3	0.14
Creatinine	69.1±5.5	71.0±5.6	1.9±7.4	0.32
Sodium	0.1±2.8	-0.4±9.4	0.3±2.1	0.88
Potassium	26.7±10.2	27.2±9.4	0.6±10.7	0.84
Phosphate	45.2±20.8	47.8±14.2	2.7±11.8	0.17
Calcium	-20.9±17.0	-17.8±14.6	-3.0±15.5	0.27

BUN=blood urea nitrogen

rate, and online Kt/V were closely observed and recorded every 30 minutes. We found that the mean body temperature of 37°C dialysate group was increased (0.32°C) higher than in the 35°C dialysate group that was increased only 0.05°C ($p<0.01$). This finding confirmed that degree of dialysate temperature affected body temperature in the same direction (Figure 2).

Blood pressure levels were significantly different between the 2 groups. Mean SBP of 35°C dialysate group was 159.3±2.6 mmHg and of 37°C dialysate group was 152.7±4.4 mmHg ($p<0.01$). DBP of 35°C dialysate group was 66.6±1.6 mmHg and of 37°C dialysate group was 65.5±2.2 mmHg ($p<0.01$). Finally, the mean MAP of 35°C dialysate group was higher than the 37°C dialysate group (4.3±2.8 mmHg, $p<0.01$) as shown in Figure 3.

There were no significant differences of online Kt/V in any time point and ultrafiltration volume between the two dialysate temperature groups (Figure 4).

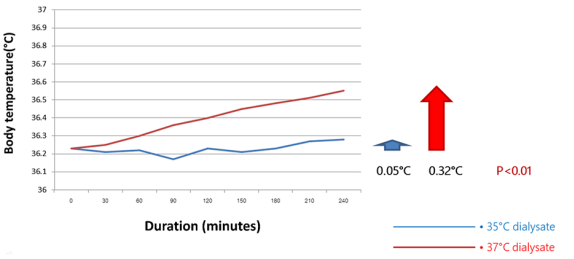

Figure 2. Mean difference of body temperature occurring in usage of different dialysis temperature.

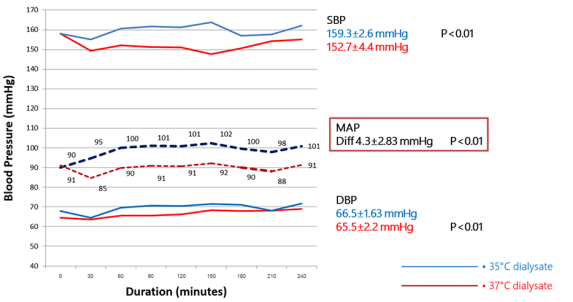

Figure 3. Mean differences of SBP, DBP and MAP among 35°C and 37°C dialysate groups.

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure

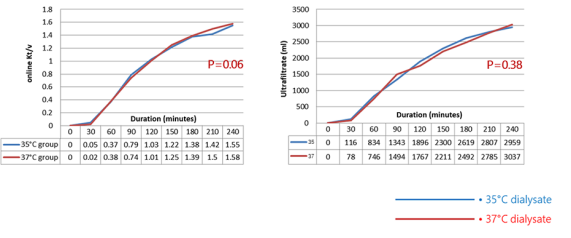

Figure 4. Mean differences of online Kt/V and ultrafiltration volume between the two dialysate temperature groups.

Adverse events

All of 27 patients and 54 HD sessions, 6 adverse events happened. Two intradialytic hypertension events were noted in each 35°C dialysate and 37°C dialysate groups with improvement by giving of antihypertensive drugs. In the 35°C dialysate group, one case shivered at 90 minutes of dialysis session improved by increase of dialysate temperature to 37°C. One event of intradialytic hypotension in the 37°C dialysate group was found and improved by decreases of dialysate temperature to 36°C and ultrafiltration rate.

There were not any life-threatening conditions and no termination of any session of dialysis because of severe adverse events.

Discussion

Uremic retention solutes have been recognized as toxins affecting several organs and causing morbidity, diminished quality of life and enhanced mortality[22,23]. Recently, the revised classification of uremic retention solutes was recommended with focusing on source of generation, molecular weight, protein-bound affinity, known toxicity, and technique or dialysis modality for removal[22-24]. B2M is a marker molecule of small middle molecules, i.e., 0.5 to 15 kilodalton weight, which has been studied and shown evidence of biological toxicity and removable by high-flux HD, high-flux HDF and expanded HD using

medium-cutoff membrane (HDx)[22-25].

The current study is the first report to compare effects of cool dialysate (35°C) and warm dialysate (37°C) on B2M removal evaluated by magnitude of %RR in the stable HD participants. The crossover randomize trial was used to reduce interpatient variation and specific statistic tests (i.e., carry over, period and sequence effect analyses) were used to prove the independent of each effect. The study findings revealed that these two dialysate temperatures contributed to the difference of increased body temperature, 0.05°C in 35°C dialysate group and 0.32°C in 37°C dialysate group, and significantly effected on B2M removal which greater in the warm dialysate group [mean difference of %RR, -9.7±10.3% (95% CI: -15.9 to -3.5%), p=0.03]. The possible explainable mechanism is warm dialysate attenuates the intercompartmental resistance by increasing blood vessel diameter and surface area of capillaries, therefore, enhancing the removal of toxins trapped in peripheral tissues into the vasculature and ultimately leading to their elimination through the dialyzers[10].

In the other hand, no significant effects of dialysate temperature on smaller molecule reductions such as urea, creatine, and electrolytes. Previous studies investigated the influence of cool dialysate on urea clearance, which no significant change was observed[8,13,26]. This lack of impact can be attributed to its small size, allowing urea to freely diffuse and rapid equilibration across cell membranes and capillaries, and may be enhanced the transport by selective urea transporters resulting in minimizing resistance to its movement and ensures efficient movement regardless of temperature changes[8,10,13,26].

Previous reports of %RR for B2M removal by various dialysis modalities were 49.7 to 57% in high-flux HD with dialyzers Kuf 40 to 55 ml/hr/mmHg[19,27,28], 74.6% for high-flux HD with dialyzers Kuf 64 ml/hr/mmHg and sieving coefficient for B2M 0.9, 72.7 to 83.2% for HDF[14,28,29], and 73.7 to 77.8% for HDx[14,29]. The present study demonstrated %RR of high-flux HD with 35°C dialysate as 63.7 to 65.7% and with 37°C dialysate 72.6 to 75.8%. Besides dialysis modality, factors related with B2M reduction and clearance which may result in differences of %RR among various studies were characteristics of dialyzer membrane, duration of HD treatment, patient body size, total ultrafiltration volume, blood flow rate, intradialytic B2M generation, renal (non-dialyzer) clearance, and post dialysis rebound of B2M[7]. Nevertheless, substantial increase of B2M reduction was found in the application of 37°C dialysate with high-flux HD quite similar to HDF and HDx.

Recent systematic reviews suggested that the vasoconstrictive effect of reduced temperature dialysis might mitigate the occurrence of intradialytic hypotension and potentially elevate MAP during the procedure[13,30]. One should also note that warm dialysate may result in lower intradialytic SBP, DBP and MAP, and so only stable HD subjects were recruited for the present trial. Although, the 37°C dialysate group has lower MAP than the 35°C dialysate group around 4.3±2.8 mmHg, $p<0.01$, there was only one event of mild symptom of hypotension and no serious complication reported. In the other way, the effect of blood pressure reduction was useful for the participants who had high intradialytic hypertension. Furthermore, the online Kt/V values and ultrafiltration volume were monitored during the study periods, although significant difference of blood pressure among the 2 groups was observed, this effect did not disturb the Kt/V and ultrafiltration of both groups.

Limitations

The present study has some limitations. First, due to the short duration of this study, the results may not be representative of longer-term effects. Second, the toxins removal was only evaluated by the reduction ratio which did not cover solute clearance and post-dialysis rebound. Third, although the body temperature was rising as the degree of dialysate temperature, the evidence of thermal-induced vasodilatation did not be proven in this trial. Fourth, the recruited participants were hemodynamical stable, the application of warm dialysate intervention in ESKD patients who have rather low blood pressure or significant heart diseases should be caution. Fifth, only 1 blood draw after period of 2 weeks may have other factors affecting outcomes. If at least 2 blood draws are taken and averaged, it should reduce more confounding factors. Sixth, although in sequence A, the numerical %RR of 35°C dialysate was lower than the 37°C dialysate group but the mean difference did not reach statistically significant which might be explained from the wider range of standard deviation of %RR at the initial period compared to the sequence B as shown in Table 2. Finally, further research should be conducted to study the long-term effect of different specific dialysate temperature profiling on mortality outcome.

Conclusion

Usage of 37°C dialysate can induce higher body temperature and increase rate reduction ratio of B2M and also slightly decrease blood pressure by no serious complication was shown compared with the 35°C dialysate group. In stable patients with moderately high blood pressure, selected groups may benefit from low accumulation of B2M and well controlled hypertension from this effect.

What is already known about this topic?

The previous study has postulated that usage of warm dialysate may increase mobilization and removal of toxins due to elevated body core temperature which augments

vasodilation, reduces peripheral resistance, enhances cardiac output and inter-compartmental mass transfer, and reduces post-dialysis rebound of toxins[10]. However, no report of proven benefit of warm dialysate on middle molecule removal in ESKD patients undergoing HD was documented.

What this study adds?

The present study is the first report to support the efficacy of warm dialysate (37°C) compared to cool dialysate (35°C) on B2M removal and blood pressure reduction in the stable HD patients.

Acknowledgements

The authors would like to thank all staff of the Center of Excellence in Kidney Diseases, Srinagarind Hospital, and the Department of Medicine, Faculty of Medicine, Khon Kaen University for research and publication support.

Funding sources

The study was supported by funding from Faculty of Medicine, Khon Kaen University and the Chronic Kidney Disease Prevention in the Northeast of Thailand (CKDNET) research funds.

Conflicts of interest

The authors declare no conflict of interest.

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