

## Cooling dialysate during in-center hemodialysis: Beneficial and deleterious effects

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### Abstract

The use of cooled dialysate temperatures first came about in the early 1980s as a way to curb the incidence of intradialytic hypotension (IDH). IDH was then, and it remains today, the most common complication affecting chronic hemodialysis patients. It decreases quality of life on dialysis and is an independent risk factor for mortality. Cooling dialysate was first employed as a technique to incite peripheral vasoconstriction on dialysis and in turn reduce the incidence of intradialytic hypotension. Although it has become a common practice amongst in-center hemodialysis units, cooled dialysate results in up to 70% of patients feeling cold while on dialysis and some even experience shivering. Over the years, various studies have been performed to evaluate the safety and efficacy of cooled dialysate in comparison to a standard, more thermoneutral dialysate temperature of 37 °C. Although these studies are limited by small sample size, they are promising in many aspects. They demonstrated that cooled dialysis is safe and equally efficacious as thermoneutral dialysis. Although patients report feeling cold on dialysis, they also report increased energy and an improvement in their overall health following cooled dialysis. They established that cooling dialysate temperatures improves hemodynamic tolerability during and after hemodialysis, even in patients prone to IDH, and does so without adversely affecting dialysis adequacy. Cooled dialysis also reduces the incidence of IDH and has a protective effect over major organs including the heart and brain. Finally, it is an inexpensive measure that decreases economic burden by reducing necessary nursing intervention for issues that arise on hemodialysis such as IDH. Before cooled dialysate becomes standard of care for patients on chronic hemodialysis, larger studies with longer follow-up periods will need to take place to confirm the encouraging outcomes mentioned here.

**Key words:** Hemodialysis; Dialysate temperature; Cool dialysate; Intradialytic hypotension; Hypotensive episodes;

Hemodynamic stability; Cool temperature dialysis

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**Core tip:** Cooled dialysate is commonly employed to reduce the incidence of intradialytic hypotension (IDH) in patients on chronic dialysis. The studies to date that have evaluated cooled dialysate are limited by small sample size and it has not become the standard of care for managing IDH. However, the small studies that exist are promising and suggest that cooling dialysate improves hemodynamic tolerability of dialysis, minimizes IDH, and exerts a protective effect over major organs including the heart and brain. More studies are needed to assess the long-term effects of cooling dialysate in this population.

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## INTRODUCTION

According to the KDOQI Clinical Practice Guidelines, intradialytic hypotension (IDH) is defined as a symptomatic decrease in systolic blood pressure of  $\geq 20$  mmHg or a decrease in mean arterial pressure (MAP) by 10 mmHg with symptoms being characterized by abdominal discomfort, nausea, vomiting, muscle cramps, dizziness, restlessness, and anxiety, amongst others<sup>[1]</sup>. It occurs in approximately 20%-30% of dialysis sessions<sup>[2]</sup> and is the most frequent complication of renal replacement therapy<sup>[3]</sup>. IDH is multifactorial in etiology but is largely attributed to the rapid reduction of blood volume that occurs with ultrafiltration and the inadequate cardiovascular response to the reduction in blood volume<sup>[2,4]</sup>. Populations predisposed to IDH include the elderly and those with diabetes and cardiovascular diseases<sup>[3]</sup>.

IDH is an independent risk factor for mortality in patients on hemodialysis<sup>[5,6]</sup> and may negatively affect their quality of life<sup>[7]</sup>. It is also associated with increased morbidity including frontal lobe atrophy<sup>[8]</sup>, myocardial injury<sup>[9]</sup>, and mesenteric ischemia<sup>[10]</sup>. Nephrologists employ various methods on dialysis to minimize IDH including sodium modeling, ultrafiltration profiling, addition of calcium or bicarbonate to the dialysate bath, and dialysate cooling. While each method has its positive and negative attributes, the focus of this review will be on dialysate cooling.

Extracorporeal cooling of blood on dialysis first came about over three decades ago when it was noted to curb the incidence of IDH. Since then, it has been employed as a measure to mitigate IDH although it has not become standard of practice in chronic hemodialysis

units.

## DISCUSSION

### **Core body temperature and the effect of cooled dialysate**

Humans keep their core body temperature (CBT) within a narrow range. When CBT rises, the body increases peripheral blood flow or initiates sweating in an attempt to remove heat from the body by convection or radiation, respectively. Shivering is usually an involuntarily thermoregulatory mechanism employed by the body to generate heat when CBT falls. While on dialysis, the dialysate temperature is set to an arbitrary standard of 37 °C (98.6 °F) in an effort to achieve a "normal" CBT and maintain isothermia. However, a significant amount of variability exists amongst individuals when it comes to CBT. First, CBT follows a circadian pattern that peaks between 4 and 9 pm and nadirs between 2 and 8 am<sup>[11,12]</sup>. CBT tends to be lower in elderly individuals<sup>[12]</sup>, higher in women than in men, and is highest in black women<sup>[13]</sup>. In hemodialysis-dependent individuals, CBT is usually lower than in the non-dialysis population<sup>[11,14]</sup>, with nearly 40% having a CBT less than 36.5 °C<sup>[15]</sup> compared to the mean CBT of 37 °C (range, 36.2 °C to 37.5 °C) in non-dialysis dependent individuals<sup>[12]</sup>. The importance of this becomes evident when one considers that even a slight change in CBT on dialysis initiates thermoregulatory mechanisms which may be detrimental on dialysis. For example, a supraphysiologic dialysate temperature, such as 37 °C, could raise the CBT in any given individual resulting in vasodilation and consequent cardiovascular instability. The vasodilation may be in direct competition with the expected vasoconstriction which occurs in the setting of ultrafiltration and could further lead to hemodynamic compromise.

Since supraphysiologic dialysate temperature was viewed as suboptimal and potentially detrimental, the idea that subphysiologic dialysate temperature might be beneficial arose, specifically in those individuals that suffered from IDH. Cooled dialysate temperature was postulated to be beneficial for the following reasons: First, it avoided heat accumulation and hence counterproductive thermoregulatory vasodilation; second, it likely led to a catecholamine surge which induced both peripheral vasoconstriction and cardiac inotropy<sup>[16]</sup>. However, at the time various potential consequences surrounding cooled dialysate remained unclear. Would dialysis adequacy be inferior? Would it cause prolonged vasoconstriction potentially placing vulnerable vascular beds at risk for ischemia? Would patients be tolerant of the cooled CBT on dialysis? Finally, would it be effective at minimizing IDH?

Various studies have since been performed to address the above issues. Kaufman *et al.*<sup>[17]</sup> aimed to evaluate the efficacy of cooled dialysate during short-time, high Kt/V dialysis treatments. He postulated that cooled dialysate might increase urea compartmentalization during dialysis

treatment leading to increased urea rebound post-dialysis and hence decrease dialysis efficacy. The study was performed in 15 patients who underwent a total of 56 dialysis sessions. Each participant served as their own control. Dialysate temperatures were adjusted to either lower CBT (cooled dialysis) or keep CBT at a thermoneutral temperature. Dialysate cooling resulted in  $-266 \pm 15$  kJ heat-energy exchange per treatment whereas thermoneutral dialysis averaged  $5 \pm 31$  kJ per treatment; dialysate temperature averaged  $35.7^\circ\text{C} \pm 0.02^\circ\text{C}$  and  $37.1^\circ\text{C} \pm 0.02^\circ\text{C}$ , respectively. Cooled dialysis resulted in statistically greater increases in the peripheral vascular resistance index and MAP. It also reduced the maximum intradialytic fall in MAP and necessary interventions by staff to address hypotensive symptoms. There were no statistical changes in blood volume, cardiac index, urea rebound, or effective Kt/V. The authors concluded that cooling dialysate stabilized hemodynamics during dialysis, reduced the number of staff interventions required to address IDH symptoms, and did so without affecting the efficacy of high-efficiency dialysis. A systematic review that evaluated 22 studies comprising of 408 patients has since concluded that using cooling dialysate temperature does not reduce dialysis adequacy<sup>[18]</sup>.

Ayoub *et al.*<sup>[19]</sup> aimed to gauge patient perception of cooled dialysate. Five patients known to have IDH were dialyzed for three sessions using cooled dialysate ( $35^\circ\text{C}$ ) followed by another three sessions with dialysate temperature set at  $36.5^\circ\text{C}$ . The same was done in a second group of five patients known to have stable blood pressures during and after their dialysis sessions. Their results demonstrated that cooling dialysate resulted in a statistically significant increase in ultrafiltration in the group known to have IDH. This group also experienced significantly higher intra- and post-dialysis MAPs with cooled dialysate. While the IDH-prone group had no episodes of hypotension with cooled dialysate, they had a total of seven episodes of hypotension with neutral temperature dialysate, all requiring nursing intervention ( $P < 0.001$ ). There was no statistical difference in intradialytic pulse rates between the two groups nor did cooling dialysis have an effect on urea removal between the two groups. Patients' perception about cooled dialysis was assessed by a questionnaire designed specifically for this study. It comprised of the following questions: "How did you feel while being dialysed on cool temperature? Compared with normal temperature dialysis of  $36.5^\circ\text{C}$ , did you feel any differences while being dialysed on cool temperature? If yes, what were the differences? Would you like to continue cool temperature dialysis?" The results of the questions were as follows: 80% of patients felt more energetic after being dialyzed with cooled dialysate; 80% felt a dramatic improvement in their general health with cooled dialysate; 80% requested to always be dialyzed with cooled dialysate; 20% reported feeling cold during dialysis. The authors concluded that for patients prone to IDH, cooled dialysate improved hemodynamic stability during and after dialysis,

improved tolerance of dialysis, reduced the number of nursing interventions required to address IDH, and had an overall positive impact on patients' energy and activities of daily living. This is the only study to date that has specifically assessed patient perception of cooled dialysate temperature. However, a systematic review by Selby *et al.*<sup>[18]</sup> pooled the results of five studies in which symptoms were reported during cooled dialysis. Their analysis demonstrated that patients undergoing cooled dialysis were 1.98 (95%CI: 0.38-3.57) times more likely to become symptomatic than patients dialyzed with standard dialysate temperatures. When the analysis omitted the study by Ayoub and Finalyson<sup>[19]</sup> due to milder symptoms being reported compared to the other four studies, the results were non-significant with symptoms occurring 1.5 (95%CI: -0.2-3.2) times more often with cooled dialysis than during standard dialysis.

A similar study by Jost *et al.*<sup>[20]</sup> compared cooled dialysate to thermoneutral dialysate to specifically evaluate its efficacy on "problem" patients. The design used a double-blinded, cross-over protocol to evaluate 12 patients, six of whom were prone to IDH and six known to have large interdialytic weight gains defined as consistently gaining  $> 4$  kg in the interdialytic period. Each patient served as their own control and was randomly assigned to one session of dialysis at  $35^\circ\text{C}$  and one at  $37^\circ\text{C}$ . Results demonstrated significantly lower blood pressures at 1, 2, and 3 h of dialysis at a thermoneutral dialysate temperature when compared to the cooled dialysate temperature. A total of 18 episodes of symptomatic hypotension occurred during the study period, 16 of which occurred in the IDH-prone group. Furthermore, no episodes of symptomatic hypotension occurred during cooled dialysis ( $P < 0.01$ ). The authors concluded that cooling dialysate significantly improved hemodynamic tolerance during dialysis and also significantly reduced the incidence of IDH during dialysis in patients prone to IDH. These studies added to the literature supporting cooled dialysate as an effective way of reducing IDH.

### **Cooled dialysate compared to other modalities used to minimize IDH**

Dheenani and Henrich<sup>[21]</sup> were the first to compare cooled dialysate to other methods that are commonly employed to mitigate IDH. They used a single-blinded, cross-over protocol to evaluate 10 patients on chronic hemodialysis with a history of IDH. Patients were randomized to one week periods (three dialysis sessions) of five varying dialysis protocols performed in a random and blinded fashion. Each patient underwent four protocols commonly employed to minimize IDH in addition to a standard dialysis protocol which served as a control. The protocols were as follows: A standard dialysis group with dialysate sodium of 138 mEq/L (served as the control group), high sodium dialysate (patient dialyzed using a steady dialysate sodium of 144 mEq/L), sodium modeling using a step function design (dialysate sodium declined from 152 to 140 mEq/L in the last 30 min of

dialysis), ultrafiltration (one hour of isolated ultrafiltration in which 50% of the target weight loss was removed followed by three hours of isovolemic dialysis), and cool temperature dialysis in which dialysate was cooled to 35 °C (sodium concentration was 140 mEq/L in this group). The results revealed indistinguishable weight losses with each protocol suggesting that the volume of ultrafiltration was consistent across each protocol. However, the results demonstrated superiority of sodium modeling and cooled dialysate groups over the other groups, and multiple similarities between these two methods. Both had significantly fewer hypotensive signs and symptoms per treatment and fewer hypotensive episodes per treatment when compared with standard treatment. Both also had significantly fewer nursing interventions for IDH per treatment when compared to the ultrafiltration and control group. The nadir MAP was significantly lower in the control and ultrafiltration groups whereas the upright post-dialysis blood pressure was best preserved in the sodium modeling and cooled dialysate groups. Sodium modeling was tolerated by all but one patient who developed hypertension, headache, and nausea; 6 out of the 10 reported increased thirst sensation however this did not translate into increased interdialytic weight gain during the one week follow-up period. Cooled dialysate, however, was not well tolerated. Seven of 10 patients reported a "cold" sensation and two patients were noted to be shivering on dialysis.

A similar study by Rezki *et al.*<sup>[22]</sup> evaluated 16 patients in a two-phase protocol. The first phase consisted of three standard HD sessions with a sodium concentration of 140 mEq/L with dialysate temperature at 37 °C and served as the control for each patient. During the second phase, patients were dialyzed successively under the following conditions: Fixed sodium dialysate concentration at 144 mEq/L, sodium modeling from 152 to 138 mEq/L, one hour of ultrafiltration alone followed by three hours of standard dialysis, dialysis with cooled dialysate ( $T < 37\text{ °C}$ ), and a combination of sodium modeling with cooled dialysate. When compared to the control protocol, there was a statistically significant decrease in the signs and symptoms of hypotension and in the incidence of IDH when patients were dialyzed with sodium modeling, cooled dialysate, or the combination protocol. When compared to the control protocol, fewer medical staff interventions were required when patients were dialyzed with the combination protocol or cooled dialysate. There was no increase in subjective thirst or in interdialytic weight gain when a protocol employing sodium modeling was performed. In this study, four of the 16 patients noted shivering when dialyzed with cooled dialysate.

Both of these studies suggest that cooling dialysate temperature is as effective a method as sodium modeling when it comes to mitigating IDH. They also suggest that cooling dialysate may be poorly tolerated and associated with patient discomfort on HD. However, sodium modeling has been associated with a number of side effects including worse hypertension and increased

interdialytic weight gain due to increased thirst<sup>[23]</sup>. Whether one method is superior at reducing IDH or is better tolerated than the other remains to be seen in a larger trial with longer follow-up periods.

### **Effect of cooled dialysate on vulnerable vascular beds**

One of the questions that arose when cooled dialysate was first introduced was whether vasoconstriction would also occur at an arteriolar level and potentially place vulnerable vascular beds at risk for end-organ injury. Since that time, it has become apparent that dialysis itself is a hemodynamic stressor<sup>[24]</sup> which triggers circulatory stress and consequently damages vasculature in the heart, mesentery, and brain<sup>[25-27]</sup> amongst other organs. Two recent trials demonstrated that cooled dialysate imparts a protective effect in these organs.

Eldehni *et al.*<sup>[25]</sup> hypothesized that ultrastructural injury to the white matter in the brain might be mitigated by cooling dialysate hence reducing dialysis-induced circulatory stress. This was evaluated by randomizing 38 incident dialysis patients to dialyze for 12 mo at either 37 °C or 0.5 °C below their core body temperature; the latter was determined by averaging each patient's temperature by tympanic thermometer during six sessions prior to commencing the trial. An individualized temperature was chosen as it is thought to be better tolerated than an arbitrary temperature of 35 °C<sup>[28]</sup>. A form of magnetic resonance imaging (MRI) called diffusion tensor imaging (DTI) was used to evaluate the structural integrity of the brain white matter at baseline and after 12 mo of thrice-weekly dialysis. DTI was chosen as an imaging modality as it has previously been used to detect clinically significant changes in cerebral small vessel disease<sup>[29]</sup>. Additionally, MAP extrema points were measured over the course of 12 mo. MAP extrema points measure the frequency and amplitude required to maintain optimal organ perfusion; higher extrema points correlate with high variation in organ perfusion and translates to detrimental perfusion of vulnerable vascular beds<sup>[25,30]</sup>. After 12 mo, patients dialyzed at 37 °C exhibited patterns of ischemic brain injury on MRI that were not noted in the cooled dialysate group. Additionally, patients dialyzed at 37 °C had a notable worsening of their MAP extrema points that was not seen in the cooled dialysate group. Both of these results were statistically significant. The authors concluded that cooling dialysate minimized injurious perfusion of cerebral vascular beds and consequently decreased the degree of brain injury noted on DTI. An advantage to this study is the long-term follow-up over the course of one year. However, despite having a larger sample size than in earlier studies evaluating the effects of cooled dialysate, it was still limited by a small sample size. Additionally, the study suffered from a high dropout rate of 47.9%, although this was primarily due to difficulty in recruiting patients on incident HD; there were no dropouts reported as a result of the intervention.

Odudu *et al.*<sup>[24]</sup> used the same patient population and study design as Eldehni *et al.*<sup>[25]</sup> to evaluate whether cooled dialysate would have cardioprotective effects



over the course of a 12 mo follow-up. Fifty-four incident dialysis patients were randomized to a dialysate temperature of either 37 °C or 0.5 °C below their core body temperature and followed for 12 mo. Tagged cardiac magnetic resonance imaging was performed at baseline and at 12 mo; the imaging modality was chosen for its high reproducibility and use as a reference standard technique to evaluate regional left ventricular (LV) strain. While there was no statistically significant change in the study's primary outcome, change in resting ejection fraction, there were multiple significant secondary outcomes of note. The cooled dialysate group experienced a significant reduction in both LV mass as well as LV end-diastolic volumes. The control group had a significant reduction in peak systolic strain, diastolic function, and segmental LV strain whereas these functions were preserved in the cooled dialysate group. As markers of subclinical cardiomyopathy, these findings suggest that cooled dialysate had a protective cardiac effect over the one year study period. Lastly, aortic distensibility, an independent marker for future cardiovascular events, was also preserved in the cooled dialysate group and significantly decreased in the control group. Whether these findings suggest that cooled dialysate may one day be linked to a decreased risk of cardiovascular events in the dialysis population remains to be seen.

## CONCLUSION

Cooling dialysate first came into practice three decades ago after it was noted to curb the symptoms of patients suffering from IHD on dialysis. Since then, many benefits of cooled dialysate temperatures have come to light. Multiple studies have demonstrated improved hemodynamic tolerance on dialysis specifically in patients prone to IDH without any adverse effect on dialysis adequacy. It is an inexpensive intervention that also reduces the frequency of nursing involvement to address IDH in patients on chronic hemodialysis. More recently, studies suggest that one year of cooling dialysate temperature in incident dialysis patients mitigates features of subclinical cardiomyopathy and ischemic brain injury when compared to patients dialyzed at the standard 37 °C.

While the cooler temperatures may cause discomfort in some patients, recent studies suggest that a temperature of 0.5 °C below an individual's CBT is better tolerated than an arbitrary temperature of 35 °C. Additionally, Ayoub and Finlayson<sup>[19]</sup> demonstrated that cooled dialysate may actually improve a patient's energy following dialysis, and in their cohort of patients, individuals requested to be dialyzed with cooled dialysate temperatures following the study. Finding a "sweet spot" for cooled dialysate may allow for increased patient satisfaction and in turn, improve patient compliance with dialysis. The advantages and disadvantages of cooling dialysate are summarized in Table 1.

Unfortunately, all of the studies performed to date on

**Table 1 Advantages and disadvantages of cooling dialysate temperatures**

Advantages	Disadvantages
Improved hemodynamic tolerance during and after dialysis	Patient discomfort
Improved patient energy	Shivering
Preservation of vulnerable vascular beds (subclinical cardiomyopathy and ischemic brain injury)	
Fewer nursing interventions needed	

cooled dialysate have been limited by small sample sizes. Larger studies are needed in order to be generalizable to a greater portion of the chronic hemodialysis population. From a patient perspective, it will be important to study perception and comfort with dialysis at cooler temperatures since there appears to be a trend toward a higher incidence of symptoms with cooled dialysis when compared to standard dialysis. Studies with longer follow-up times would be useful to evaluate the effects of sodium modeling and cooled dialysate on incidence of IDH as well as its effects on interdialytic weight gain and hypertension. Longer follow-up would also allow for assessment of the effects of cooled dialysate on vulnerable vascular beds and their clinical correlates, for example cardiovascular events, dementia, memory, executive function, *etc.* Encouraging results in such studies would have the potential to change the standard of care in patients on chronic hemodialysis.

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