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A four-stream method for providing variable dialysis fluid bicarbonate concentrations for bicarbonate-based dialysis fluid delivery systems

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Abstract

Background: Hemodialysis corrects metabolic acidosis by transferring bicarbonate or bicarbonate equivalents across the dialysis membrane from the dialysis fluid to the plasma. With the conventional three-stream bicarbonate-based dialysis fluid delivery system, a change in the bicarbonate concentration results in changes in the other electrolytes. In practice, the dialysis machine draws either a little less or more from the bicarbonate concentrate and a little more or less from the acid concentrate, respectively in a three-stream delivery system. The result not only changes the bicarbonate concentration of the final dialysis fluid but also causes a minor change in the other ingredients.

Methods: We propose a four-stream bicarbonate-based dialysis fluid delivery system consisting of an acid concentrate, a base concentrate, a product water, and a new sodium chloride concentrate.

Results: By adjusting the flow rate ratio between the sodium chloride and sodium bicarbonate concentrates, one can achieve the desired bicarbonate concentration in the dialysis fluid without changing the concentration of sodium or ingredients in the acid concentrate. The chloride concentration mirrors the change in bicarbonate but in the opposite direction.

Conclusion: A four-stream, bicarbonate-based dialysis fluid delivery system allows the bicarbonate concentration to be changed without changing the other constituents of the final dialysis fluid.

KEYWORDS

acid concentrate, base concentrate, bicarbonate, dialysate, dialysis fluid, end stage kidney disease, fluid delivery system, four-stream dialysis, hemodialysis

1 | INTRODUCTION

Hemodialysis corrects metabolic acidosis, a cardinal manifestation of advanced renal failure.^{1–3} The base contained in the dialysis solutions consists of sodium bicarbonate

or sodium salts of bicarbonate precursors such as lactate or acetate. When the dialysis fluid contains a bicarbonate precursor, this substance moves from the dialysis fluid into the blood compartment while bicarbonate moves from the blood compartment into the dialysis fluid. The

Ingredients	Sodium chloride concentrate (S)	Bicarbonate concentrate (B)	Acid concentrate (A)
Sodium chloride (NaCl)	968	–	2835
Sodium bicarbonate (NaHCO ₃)	–	968	–
Potassium chloride (KCL)	–	–	90
Calcium chloride (CaCl ₂ ·2H ₂ O)	–	–	56.25
Magnesium chloride (MgCl ₂ ·6H ₂ O)	–	–	16.875
Dextrose (C ₆ H ₁₂ O ₆ ·H ₂ O)	–	–	252
Acids			
Acetic acid (CH ₃ COOH)	–	–	180
Citric acid (C ₆ H ₈ O ₇)	–	–	108
Sodium diacetate (NaH{C ₂ H ₃ O ₂ }) ₂)	–	–	180

Note: An additional 4 mmoles/L of sodium acetate become available if sodium diacetate is used.

body converts the bicarbonate precursor to bicarbonate during and after the dialysis treatment. If the bicarbonate precursor conversion to bicarbonate fails to keep pace with bicarbonate loss, patients will develop worsening of metabolic acidosis.

When the dialysis fluid contains sodium bicarbonate, bicarbonate diffuses across the dialyzer membrane from the compartment with the higher concentration to the compartment with the lower concentration until it reaches equilibrium. Many patients on maintenance hemodialysis generally have low to normal pre-dialysis plasma total carbon dioxide levels. In these patients, bicarbonate, which is higher in the dialysis fluid than in plasma, diffuses from the dialysis fluid into the blood compartment resulting in a net gain in bicarbonate. A net gain of bicarbonate during dialysis was demonstrated in a study in which patients dialyzed with higher dialysis fluid bicarbonate concentrations (35 compared to 30 or 25 mmoles/L) had higher post-dialysis plasma bicarbonate levels.³ Bicarbonate moves from the blood compartment to the dialysis fluid resulting in a net loss of bicarbonate if its concentration is higher in plasma than in the dialysis fluid.

Clinical situations occur that mandate adjusting the dialysis fluid bicarbonate concentration ([HCO₃[–]]_{df}). The interplay among the acid concentrate, sodium bicarbonate concentrate, and product water in the current three-stream dialysis fluid delivery system mandates a change in the concentrations of the ingredients of the acid concentrate when adjusting the bicarbonate concentration in the dialysis fluid.⁴ We propose the use of a four-stream, triple-concentrate, bicarbonate-based dialysis fluid delivery system in which one can alter [HCO₃[–]]_{df} without changing

TABLE 1 Composition, in mmoles/L, of the ingredients of the sodium chloride concentrate (**S**), the bicarbonate concentrate (**B**), and the acid concentrate (**A**) of the 45×, four-stream, bicarbonate-based K⁺ 2, Ca⁺⁺ 2.5 dialysis fluid

the concentrations of the other ingredients of the dialysis fluid, except chloride.

2 | METHODS

2.1 | A variable dialysis fluid sodium approach using a four-stream method

We previously proposed a novel four-stream, triple-concentrate, bicarbonate-based dialysis fluid delivery system to expand the range of sodium concentration in the dialysis fluid ([Na]_{df}) without changing the concentrations of the ingredients delivered from the acid and bicarbonate concentrates to the final dialysis fluid.⁵ In this system, a 45×, four-stream, triple-concentrate, bicarbonate-based dialysis fluid delivery system consists of an acid concentrate stream, **A**; a sodium bicarbonate concentrate stream, **B**; a sodium chloride concentrate stream, **S**; and a product water stream, **W**.

Table 1 shows the composition of streams **S**, **A**, and **B**. The normal flow rate ratios for **W**:**S**:**A**:**B** are 40.56:1.72:1:1.72, respectively (totaling 45 or 45×). At these flow rate ratios, the components of the dialysis fluid prior to any chemical reactions in this fluid have the following concentrations, all in mmoles/L for a typical “2 potassium, 2.5 calcium” bath: components of the sodium chloride concentrate (**S**), sodium 37 and chloride 37; components of the acid concentrate (**A**), sodium 63, potassium 2, calcium 1.25, magnesium 0.375, acetic acid 4, chloride 68.25, and dextrose 5.6; and components of the sodium bicarbonate concentrate (**B**), sodium 37 and bicarbonate 37.

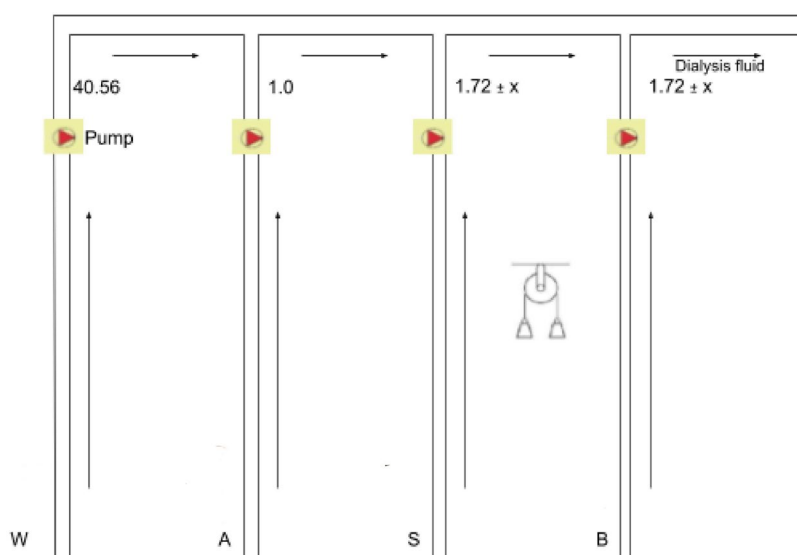
At the **W:S:A:B** flow rate ratios of 40.56:1.72:1:1.72, the concentration of sodium in the dialysis fluid is 137 mmoles/L and stream **B** delivers to the dialysis fluid a bicarbonate concentration of 37 mmoles/L. The co-existing acetic acid, 4 mmoles/L in concentration and commonly provided by many stream **A** concentrates, down titrates the final $[\text{HCO}_3^-]_{\text{df}}$ to 33 mmoles/L. An electronic pulley-like mechanism, which sits between the **W** and **S** streams and changes the proportions of sodium chloride concentrate and water in the dialysis fluid without changing the proportions of the acid or base concentrates, enables $[\text{Na}]_{\text{df}}$ to vary without affecting the ingredients from the bicarbonate or acid concentrates.⁵

2.2 | A variable dialysis fluid bicarbonate approach using a four-stream method

Using the same four-stream, triple-concentrate, bicarbonate-based dialysis fluid delivery system described above, the range of $[\text{HCO}_3^-]_{\text{df}}$ can be expanded without changing the levels of ingredients from an acid concentrate (**A**). An electronic pulley-like mechanism sitting between the sodium chloride (**S**) and sodium bicarbonate (**B**) concentrate streams allows the desired change in $[\text{HCO}_3^-]_{\text{df}}$ without a change in $[\text{Na}]_{\text{df}}$.

To change the $[\text{HCO}_3^-]_{\text{df}}$, the flow rate of **B** changes one way, and that of **S** changes by the same magnitude but in the opposite direction. For example, to increase $[\text{HCO}_3^-]_{\text{df}}$, the flow rate of **B** increases by x , and the flow rate of **S** decreases by x (Figure 1). The variable change in flow rates, represented by x , allows $[\text{HCO}_3^-]_{\text{df}}$ to change. The new flow rate ratio for **W:S:A:B** is 40.56:(1.72 - x):1:(1.72 + x) (totaling 45 or 45 $\times$). Similarly, to decrease $[\text{HCO}_3^-]_{\text{df}}$, the flow rate of **B** decreases by x , and the flow rate of **S** increases by x (Figure 1). The new **W:S:A:B** flow rate ratio is 40.56:(1.72 + x):1:(1.72 - x) (totaling 45 or 45 $\times$). In both situations, the dialysis fluid concentrations of the ingredients in the **A** concentrate remain unchanged. Table 2 shows the composition of the dialysis fluid when the **B** and **S** flows of the new four-stream system change by the same rate and in opposite directions. The supplement shows the calculations for the values in Table 2.

Note that the chloride concentration of the dialysis fluid, which is 105.25 mmoles/L (68.25 mmoles/L from flow stream **A** and 37 mmoles/L from flow stream **S**) at a **W:S:A:B** flow rate ratio of 40.56:1.72:1:1.72, will change by the same amount in the opposite direction of $[\text{HCO}_3^-]_{\text{df}}$ when the flow rate ratio **S:B** changes. In the above examples, with the use of a pulley like-mechanism between the **S** and **B** concentrates, $[\text{Na}]_{\text{df}}$ remains unchanged when $[\text{HCO}_3^-]_{\text{df}}$ changes.



The sign before x above should always be opposite for **S** and **B**.

FIGURE 1 How to increase or decrease the dialysis fluid bicarbonate concentration. **A** = acid concentrate stream; **B** = base concentrate stream; **S** = sodium chloride concentrate stream; **W** = product water stream; x = variable amount needed to achieve the desired final dialysis fluid bicarbonate concentration. Δ represents a pump; P represents a pulley. Increasing the dialysis fluid bicarbonate concentration occurs by increasing the flow rate ratio of **B** by x and decreasing that of **S** by x . The **W:S:A:B** flow rate ratio is 40.56:(1.72 - x):1:(1.72 + x) (totaling 45 or 45 $\times$). Decreasing the dialysis fluid bicarbonate concentration occurs by decreasing the flow rate ratio of **B** by x and increasing that of **S** by x . The **W:S:A:B** flow rate ratio is 40.56:(1.72 + x):1:(1.72 - x) (totaling 45 or 45 $\times$)

TABLE 2 Flow rate ratios **W:S:A:B** and composition (in mmol/L) of the 45×, four-stream, triple-concentrate, bicarbonate-based $K^+ 2$, $Ca^{++} 2.5$ dialysis fluid when the flow rate ratio for **B** decreases or increases by $\pm x$ with reciprocal changes in the flow rate ratio for **S**

Flow rate ratios for W : S: A: B								
x-value	B	−0.75	−0.5	−0.25	0	+0.1	+0.15	+0.2
x-value	S	+0.75	+0.5	+0.25	0	−0.1	−0.15	−0.2
Flow rate ratios	W	40.56	40.56	40.56	40.56	40.56	40.56	40.56
	S	2.47	2.22	1.97	1.72	1.62	1.57	1.52
	A	1	1	1	1	1	1	1
	B	0.97	1.22	1.47	1.72	1.82	1.87	1.92
Bicarbonate ^a		20.9	26.2	31.6	37	39.1	40.2	41.3
Sodium		137	137	137	137	137	137	137
Chloride		121.4	116.0	110.6	105.3	103.1	102.0	100.9
Potassium		2	2	2	2	2	2	2
Calcium		1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium		0.375	0.375	0.375	0.375	0.375	0.375	0.375
Acetic acid		4	4	4	4	4	4	4
Dextrose		5.6	5.6	5.6	5.6	5.6	5.6	5.6

^aBicarbonate concentration in the dialysis fluid prior to any chemical reactions. The acid component of the **A** stream titrates an equivalent amount of the sodium bicarbonate delivered by the **B** stream and the final bicarbonate concentration in the dialysis fluid is lower than its initial concentration. For example, the final dialysis fluid bicarbonate concentration is 4 mmol/L lower than the concentration delivered by stream **B** when acetic acid at a level of 4 mmol/L is used in stream **A**. After the above titration, 4 mmol/L of sodium acetate are formed. After their transfer in blood, this sodium acetate is metabolized and the freed sodium reconstitutes the base titrated in the dialysis fluid. When one orders a “pre-reaction” $[HCO_3^-]_{df}$ of 37 mmol/L, the order is equivalent to a total buffer capacity of 37 mmol/L, including a “post-reaction” $[HCO_3^-]_{df}$ of 33 mmol/L and a “post-reaction” sodium acetate of 4 mmol/L.⁴

3 | DISCUSSION

The ideal dialysis fluid delivery system should allow the clinician to optimize the final plasma bicarbonate concentration, correcting metabolic acidosis and avoiding metabolic alkalosis.⁶ Systemic consequences of chronic metabolic acidosis include increasing protein catabolism, decreasing protein synthesis, increasing insulin resistance, decreasing an elevated plasma leptin level associated with chronic renal failure, increasing β_2 -microglobulin accumulation, causing hypertriglyceridemia, and increasing osteoclast and parathyroid hormone activity.^{7,8} The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend maintaining pre-dialysis plasma bicarbonate levels at or above 22 mmol/L.⁹ Metabolic alkalosis immediately post-dialysis has adverse clinical outcomes. Cardiac arrhythmias, respiratory suppression, hypotension, and muscle cramps were noted acutely, and vascular or metastatic calcification was a chronic detrimental effect of metabolic alkalosis in one study.³ The value of $[HCO_3^-]_{df}$ provided in routine hemodialysis sessions varies widely. For example, in the Dialysis Outcomes and Practice Patterns Study (DOPPS) mean $\pm$ standard deviation $[HCO_3^-]_{df}$ was 35.5 ± 2.7 mmol/L, ranging from 32.2 ± 2.3 mmol/L in Germany to 37.0 ± 2.6 mmol/L in the United States.¹⁰ In this study, post-dialysis metabolic alkalosis due to

prolonged exposure to higher $[HCO_3^-]_{df}$ values was associated with increased mortality risk.¹⁰

The $[HCO_3^-]_{df}$ level from a conventional three-stream bicarbonate delivery system ranges from 20 to 40 mmol/L for Fresenius machines.¹¹ The $[HCO_3^-]_{df}$ level from a four-stream bicarbonate delivery system ranges from 24 to 38 mmol/L for Gambro/Baxter machines.¹² Gambro was the first to add a fourth compartment of sodium chloride to the hemodialysis dialysate delivery system.¹³ After Baxter acquired Gambro, Baxter established the Bicart Select Combi-pak® in the mid-2010s. This system allows one to add sodium chloride to dialysis fluid from dry sodium chloride (SelectCart®) component and change the concentration of bicarbonate in the final dialysis fluid without changing minor electrolytes. In 2012, a Japanese group filed a patent with the European Patent Specification describing a system similar to ours, with four streams consisting of an acid concentrate, product water, a bicarbonate concentrate, and a saline solution.¹⁴ This system allows the bicarbonate concentration of dialysis fluid to be adjusted without changing the concentrations of other metal ions such as potassium and calcium. However, the patent lacks details about the exact ingredients in each of the concentrates or how to make changes in $[HCO_3^-]_{df}$. In theory, the range of $[HCO_3^-]_{df}$ that can be provided by our new four-stream system is quite wide. However, we recommend only the use of



a conventionally recommended safe $[\text{HCO}_3^-]_{\text{df}}$ range of 20–40 mmol/L.^{11,12} In 2016, Lew et al published an abstract in the American Society of Nephrology annual meeting, describing a similar system.¹⁵

The chloride concentration in the dialysis fluid can be higher than physiological with the use of low $[\text{HCO}_3^-]_{\text{df}}$ (Table 1). Nevertheless, dialysis fluid chloride concentration provided by this system tends to be lower than its concentration in 0.9% saline (154 mmol/L). Recent evidence suggests that solutions containing high chloride concentrations can have adverse consequences. In a study of more than 15 000 patients requiring critical care, the balanced solution group had lower mortality, lower need for renal replacement therapy, and lower frequency of persistent renal dysfunction than the group receiving 0.9% saline.¹⁶ The balanced solution vs saline in intensive care study (BaSICS), a multicenter trial, explored whether balanced salt solutions are safer than saline in critical care patients.¹⁷ The results of this study are pending. Dialysis fluid from the four-stream system presented here has a lower chloride concentration than in 0.9% saline and a dialysis session lasts only for a few hours. It is unlikely that there would be adverse consequences of the high chloride concentration in the dialysis fluid under these circumstances.

A patient requiring hemodialysis to correct a complex acid-base disorder will most likely be in an intensive care unit with known simultaneous blood gas and electrolyte results to assist in tailoring the dialysis prescription. Blood gas and electrolyte values obtained during and post-treatment assure achieving the desired goal. The machine should be reset to a “default” setting at the end of a treatment and when preparing the machine for each patient. This should be a critical part of each hemodialysis session's protocol.

Optimal dialysis fluid pH ranges between 6.8 and 7.8.¹⁸ The range of the pH of the dialysis fluid will be from 6.70 to 7.05 when stream A contains acetic acid at a concentration of 4 mmol/L and the range of $[\text{HCO}_3^-]_{\text{df}}$ before any chemical reactions are 20 to 40 mmol/L (16 to 36 mmol/L after down titration by the acetic acid).

In summary, the bicarbonate concentration on the dialysis fluid can be adjusted by dialing the desired value on the machine. In practice, the dialysis machine draws either a little less or more from the bicarbonate concentrate and a little more or less from the acid concentrate, respectively, in a three-stream delivery system. The result not only changes the bicarbonate concentration of the final dialysis fluid but also causes a minor change in the other ingredients. In order to avoid changes in the concentration of the other constituents of the final dialysis fluid, a fourth concentrate containing only sodium chloride allows changes in the bicarbonate concentration of the dialysis fluid without making other changes (except chloride) as demonstrated by our four-stream delivery system.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept/design: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing. Data analysis/interpretation: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing. Drafting article: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing. Critical revision of the article: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing. Approval of article: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing. Data collection: Susie Q. Lew, Ramin Sam, Antonios H. Tzamaloukas, and Todd S. Ing.

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SUPPORTING INFORMATION

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