Combinatorial CRRT Fluid K^+ and HCO_3^- Personalization Without Spiking Bags

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Purpose

In the era of sophisticated CRRT machines with integrated citrate- and Ca-pumps and bicarbonate (Bic)-based Ca-free CRRT fluids, the next challenges of state-of-art CRRT-RCA delivery include the ability to provide sterile CRRT fluids customized for the patient's needs. In our experience, custom Bic and potassium (K) levels are often requested. However, in most CRRT programs customization is limited and achieved by spiking CRRT fluid bags with electrolyte concentrates or water which creates the risk of microbial contamination and human error. On the other hand, logistics would prevent CRRT programs from stocking a multitude of different composition pre-packaged fluids, even if absent economies of scale did not force manufacturers to forgo providing a huge variety of CRRT fluid K- and Bic options. While designing “solutions” for this problem we noted that:

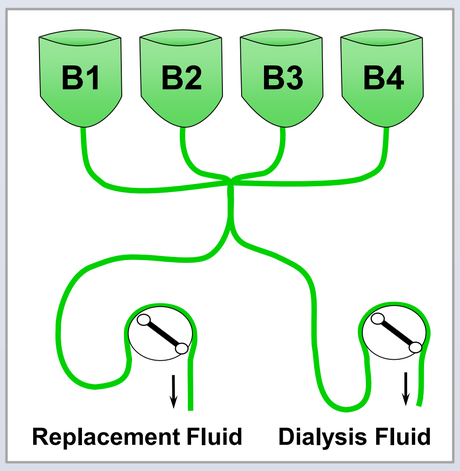
1. Several new CRRT machines can source fresh dialysate/replacement fluid from at least four 5-L bags draining simultaneously by gravity into a single, mixed fluid line which then splits into two lines to supply both the dialysate- and replacement fluid pumps
2. The huge variation of commercially available CRRT fluids allows a reasonable guess by us if a certain hypothetical CRRT fluid composition is feasible to manufacture

These observations organically lead to “Combinatorial CRRT Fluid Personalization”.

Methods

Solute		CRRT Fluid 1 0K/25Bic	CRRT Fluid 2 0K/45Bic	CRRT Fluid 3 4K/25Bic	CRRT Fluid 3 4K/45Bic
Calcium	mM	0 mM	0 mM	0 mM	0 mM
Magnesium	mM	1 mM	1 mM	1 mM	1 mM
Chloride	mM	115.5 mM	95.5 mM	119.5 mM	99.5 mM
Glucose	mM	0 mM	0 mM	0 mM	0 mM
Sodium	mM	140 mM	140 mM	140 mM	140 mM
Potassium	mM	0 mM	0 mM	4 mM	4 mM
Bicarbonate	mM	25 mM	45 mM	25 mM	45 mM
Phosphate	mM	1.1 mM	1.1 mM	1.1 mM	1.1 mM

Table: We propose the above 4 types of pre-packaged CRRT fluids which will work with Fixed Flow Ratio (FFR)-CRRT-RCA protocols (Poster 2020 CRRT Conference, Szamosfalvi & Yessayan) that achieve ≥ 75% single pass citrate removal on the filter and can be used regardless of individual ability to metabolize citrate.



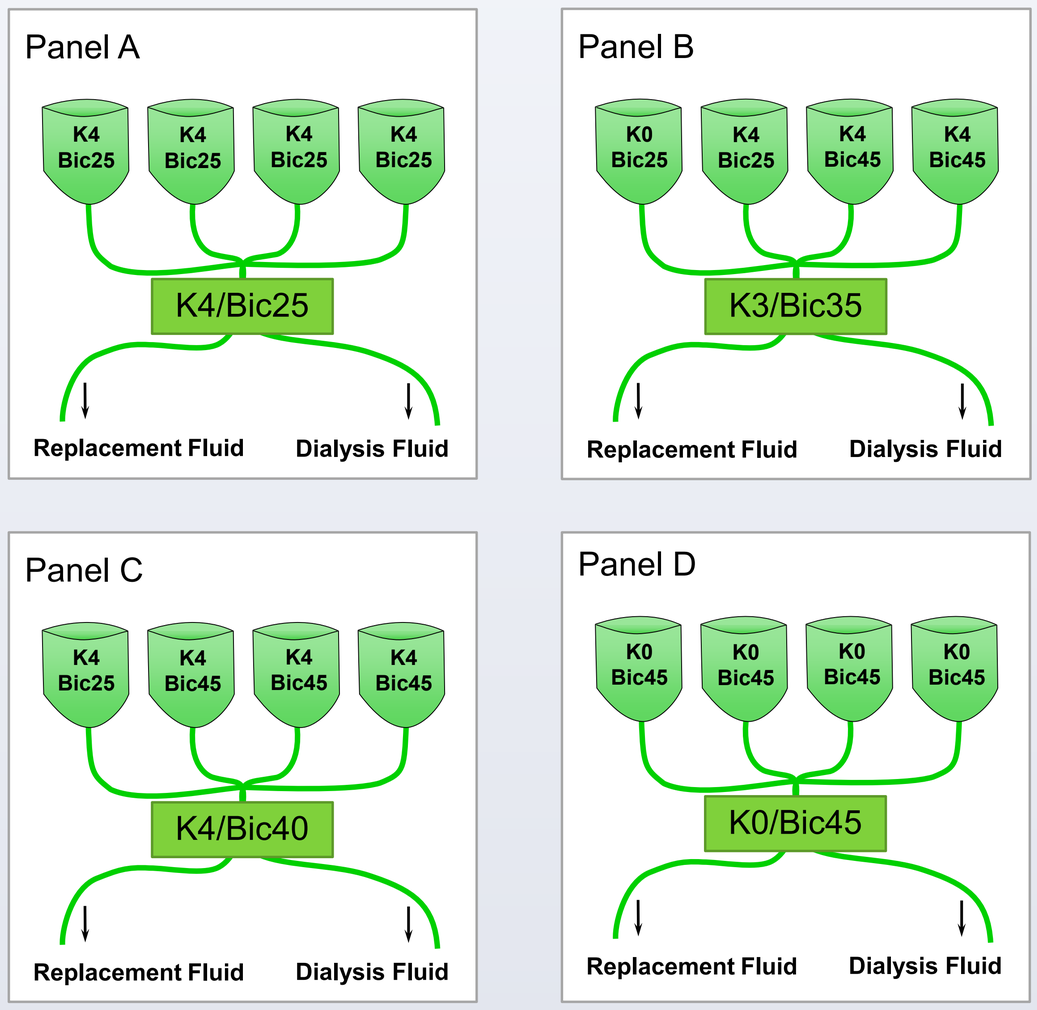
- **Total 4 bags (B1-4)** drain together and combine equally **by gravity**
- **K^+ after mixing - 5 possibilities: 0K, 1K, 2K, 3K, 4K**
- **HCO_3^- after mixing - 5** possibilities: **25Bic, 30Bic, 35Bic, 40Bic, 45Bic**
- **TOTAL independent variations: HCO3-options 5 x 5 K-options = 25**

Figure, Left Panel: During Combinatorial CRRT Fluid Personalization 4 bags of CRRT fluid drain and mix equally by gravity. **Right Panel:** The mixed CRRT fluid has a broad range of final HCO_3^-- and K-concentrations without any spiking of the CRRT fluid bags.

The personalized CRRT fluid will be an equal mix of 4 bags custom selected for positions B1-B4 (Figure). For each position we can either select a 0K- or a 4K-bag and independent of the K-content, either a 25Bic- or 45Bic-bag. The final mixed CRRT fluid may have 0/1/2/3/4K level and independently 25/30/35/40/45HCO3 level for a total combinatorial fluid option count of 5 x 5 = 25 CRRT fluids from just 4-types of stock fluids. Combined with effluent flows easily adjusted with Fixed Flow Ratio (FFR)-CRRT-RCA prescribing in the range of 1-7L/hour the final K/HCO3 fluid options should allow us to handle any clinical scenario without K- or HCO3-spiking. Mg levels at 1 mM (2 mEq/L) are optimized for CRRT-RCA when ≥90% of the total plasma Mg is dialyzable/filterable. Neutral CRRT dextrose mass balance (at normal systemic blood glucose level) with glucose-free CRRT fluids is ensured by glucose from the ACD-A and the 81.6 mM $CaCl_2$ mixed from 120 ml of 10% stock $CaCl_2$ vials with 880 ml of D50.9NS infusions (final glucose 244 mM). The CRRT fluid fixed 1.1 mM (about 3.4 mg/dL) phosphate will prevent critical hypophosphatemia and at effluent doses of ≥25 ml/kg/hr will not severely reduce phosphate removal from markedly hyperphosphatemic patients. In patients without excessive systemic bicarbonate generation from vomiting or NG suction or excessive acid generation from severe lactic acidosis, the use of mixed CRRT fluid HCO3 35 mM level will usually result in a systemic HCO3 level in the 20-25 mM range. The CRRT fluid 140 Na level will usually result in about 140-142 steady state systemic Na with FFR-CRRT-RCA (data presented as poster ASN 2019 Kidney Week). Customization of systemic steady state Na level in the range of 125-155 mM can be achieved with infusions of D5W or 3% saline, respectively at easily calculated FFR to QB to allow us to safely treat patients with current serum Na in the range of 115 to 165 mM with the described 4-types of stock CRRT fluids without spiking.

Results

The following examples show the wide variety of final CRRT fluids possible to generate from just 4 stock fluids with Combinatorial CRRT Fluid Personalization:



Panel A: This CRRT fluid will target systemic steady state K=4 mM and HCO3=15 mM. This could be a patient with acute fulminant liver failure, evolving brain edema and hyperventilation to pCO_2 20 mmHg where targeting systemic HCO3 24 would cause pH 7.6

Panel B: This CRRT fluid will cause slightly faster correction of hyperkalemia and will target systemic HCO3 around 20-24. This could be a common AKI patient with systemic K 6.2 and HCO3 18 at start. 10 hours later we could likely change to a 4K/35Bic fluid.

Panel C: This CRRT fluid will target systemic steady state K=4 mM and HCO3=30 mM. This could be a patient stabilized on CRRT with severe ARDS and pCO2 65 mmHg not expected to resolve for days where a slightly higher systemic bicarb might be desired for pH >7.25.

Panel D: This CRRT fluid with effluent flow 6L/h could remove K 30 mmol/hr and transfer HCO3 up to 150 mmol/hr into the patient if the systemic K > 6 mM and HCO3<15 mM. This could be a >100 kg patient with Burkitt’s lymphoma, severe tumor lysis with K=7 and anuric AKI as well as severe MODS with L-lactate 18 mM.

Discussion

Combinatorial CRRT Fluid Personalization as we propose is an ambitious extension of a simple practical trick that many CRRT practitioners who used 2K- and 4K-CRRT fluid bags draining together by gravity to get a 3K final fluid have utilized possibly for decades. While the idea is simple, it is very powerful and short of online CRRT fluid generation from electrolyte concentrates and ultrapure water (e.g. continuous-SLED) we are not aware of any other RRT technology solution that could afford a similar degree of K/HCO3 customization of the final CRRT fluid according to the patient’s needs. For adults, the 4x 5-L = 20L fluid batch amount is also practical as 25-30 ml/kg/hr effluent dose and average patient size >70 kg will lead to fluid use ≥2L/hr. This would allow us to adjust the final, mixed CRRT fluid composition every 10 hours without having to waste any CRRT fluid. For children in the 20-70 kg range 4 x 2.5-L = 10L fluid batch may be considered (the industry has long provided CRRT fluids in 2.5-L bags) and for infants and small children <20 kg 4 x 1-L bags might be considered. Most of the bags utilized would be of the 4K/Bic25 and 4K/Bic45 variety in about equal amounts with the 0K fluids used much less, further simplifying logistics. Bags would only have to be opened minutes prior to use, reducing waste when compared to pharmacy opened and spiked CRRT fluid management.

Conclusions

1. We demonstrated the straightforward method of Combinatorial CRRT Fluid Personalization with an empirically obvious mechanism of action.
2. We proposed 4 specific types of prepackaged CRRT fluids with compositions that should be compatible with a dual-chamber manufacturing process and terminal heat sterilization.
3. There are CRRT machines commercially available in the US and worldwide that could be used with Combinatorial CRRT Fluid Personalization without any upgrade needed.
4. Clinical studies will require at least one manufacturer to provide the 4 specific CRRT fluids we propose and a clinical user group large enough to justify custom manufacturing.
5. This Combinatorial CRRT Fluid personalization method has the potential to eliminate the need for spiking CRRT fluid bags with concentrated potassium, NaHCO3, or phosphate solutions without any compromise in optimal mixed fluid formulation for the patient.