Review Article

Basics of base in hemodialysis solution: Dialysate buffer production, delivery and decontamination

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ABSTRACT

Hemodialysis requires the use of high volumes of freshly prepared, clean dialysate to foster the removal of low molecular weight metabolites (i.e., urea) and to correct the electrolyte and acid-base imbalance of chronic renal failure. Dialysate is produced by mixing clean, AAMI grade water with both an acid and base concentrate. This purpose of this report is to describe production, mixing and delivery of the buffer component of dialysate, and to also to address the cost, safety and feasibility of producing online bicarbonate. As endotoxin contaminated dialysate has been associated with the release of key mediators in acute and chronic inflammatory diseases associated with long-term hemodialysis therapy, aspects of disinfecting a bicarbonate delivery loop are also addressed.

Key words: Bicarbonate, dialysis, dialysate

Introduction

Maintenance of a stable pH in body fluids is essential to health. Endogenous bicarbonate regeneration is necessary in order to neutralize or buffer nonvolatile acids produced by the catabolism of ingested proteins. Patients with end-stage renal disease lack the capacity to regenerate bicarbonate. As such, in order to correct metabolic acidemia, patients on dialysis require the replenishment of bicarbonate via diffusion from dialysate during hemodialysis.[1] Increased mortality is seen in patients with predialysis serum bicarbonate concentrations <17 mmol/L. With dialysis technology readily available to individualize dialysate buffer concentration, higher concentrations of predialysis serum bicarbonate can be easily achieved and thereby limit the mortality risk associated with severe acidemia.[1,2] Additionally, chronic acidemia is associated with a catabolic effect that is theorized to contribute to dysfunctional protein metabolism, malnutrition and aggravation of osteodystrophy secondary to excessive bony buffering of nonvolatile acids.[3]

Elevated serum bicarbonate >27 mmol/L prior to dialysis also associates with an increased mortality risk. However, the Dialysis Outcomes and Practice Patterns Study data showed inverse relationships between predialysis serum bicarbonate levels and nutritional factors such as serum phosphorus, albumin and markers of protein malnutrition such as normalized protein nitrogen appearance. When mortality risk was controlled for nutritional factors and dialysis efficacy, the relationship between elevated predialysis serum bicarbonate and mortality was no longer significant.[2,4] In contrast, another study using the same population suggested that increasing dialysate bicarbonate levels positively associates with mortality.[5] Based on these data and data regarding predialysis acidemia, the optimal predialysis serum bicarbonate (i.e., the group with lowest mortality risk) appears to be 22–23 mEq/L.[4]

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grade water with both an acid and base concentrate. This purpose of this report is to describe production, mixing and delivery of the buffer component of dialysate, and to also to address the cost, safety and feasibility of producing online bicarbonate. As endotoxin contaminated dialysate has been associated with the release of key mediators in acute and chronic inflammatory diseases associated with long-term hemodialysis therapy, aspects of disinfecting a bicarbonate delivery loop are also addressed.[4,6]

Dialysate Buffer

Dialysate buffers are found in the form of bicarbonate or bicarbonate precursors such as lactate, citrate or acetate. Prior to the use of more sophisticated, modern dialysate proportioning systems, sodium bicarbonate was the main dialysate buffer used in conventional hemodialysis. Originally, use of bicarbonate was hampered by technical issues. Such complexities included calcium carbonate precipitation when mixed with acid concentrate, instability of bicarbonate in solution upon exposure to the atmosphere, propensity for bacterial contamination and need for frequent mixing and immediate use.[6]

Bicarbonate as the main dialysate buffer was abandoned after Mion *et al*. described the efficacy of, and superior physicochemical properties of acetate based dialysate in 1964.[7] While acetate, *per se*, is not a buffer, it is metabolized to bicarbonate via the citric acid cycle in the human body. Acetate was simple to use and much cheaper than producing bicarbonate-based dialysate.[8] Unfortunately, use of acetate as the main buffer, particularly in high flux, high efficiency hemodialysis, was complicated by arterial hypotension, high incidence of nausea, vomiting and headache, worsened metabolic acidemia, and hypoxemia especially in susceptible individuals.[9-13] The cause of such morbidity is theorized to be a result of acetate accumulation and toxicity, stimulation of interleukin production from monocytes, slow metabolism of acetate to bicarbonate, and acute metabolic acidemia due to bicarbonate removal from the blood space.[3]

After the invention of three-stream proportioning systems, bicarbonate was again able to be used as the main dialysate buffer.[14] In a three-stream proportioning system, acid concentrate and base concentrate are mixed with AAMI grade water in ratios specific to the particular proportioning system used. Commonly used proportioning ratios (denoted as acid:base:water) are 1:1.72:42.28 (45x) and 1:1.83:34 (36.83).[15] This invention not only allowed the use of more physiologic, bicarbonate-based buffer, it eliminated many of complexities of bicarbonate-based dialysate such as calcium carbonate precipitation. Additionally, three-stream proportioning via various types of concentrate pumps provided the mechanism for individualized bicarbonate delivery to patients with varying acid:base disturbances.[16] For example, a patient with a metabolic acidosis could be dialyzed against more bicarbonate per liter of dialysate, whereas a patient with a metabolic alkalosis could be dialyzed against less.

When calculating the total delivered dialysate buffer to the patient, the nephrologist must also take into account additional buffer contribution from the acid concentrate. Acid concentrate contains acetic acid, citric acid or sodium diacetate to maintain the final dialysate pH. Organic acids from the acid concentrate consume bicarbonate from the bicarbonate concentrate, leading to an equivalent gain of sodium acetate in the final dialysate solution. Acetate, after entry into the bloodstream, will be metabolized via the citric acid cycle to an equivalent amount of bicarbonate.[8] The final amount of buffer available to the patient is thus unchanged. Similar reactions occur when citric acid is used as the organic acid in the acid concentrate, except citrate is formed (along with a very small amount of acetic acid).[17] Sodium diacetate is composed of equimolar amounts of sodium acetate and acetic acid. This compound allowed the use of dry acid concentrate, which is more favorable compared to liquid acetic acid for a variety of reasons ranging from safety to shipping cost.[8] In essence, sodium diacetate generates 2 bicarbonate equivalents after dialysis into the blood compared to 1 bicarbonate equivalent generated by acetic acid. Unless the base concentrate is adjusted accordingly by the nephrologist, the patient will be exposed to a higher buffer load than prescribed when sodium diacetate is used as the organic acid in the acid concentrate.

Despite the above-mentioned advantages of three-stream proportioning, bicarbonate buffer is still required to be produced on a daily basis due to chemical instability when exposed to the atmosphere and the propensity for bacterial contamination. Daily mixing of bicarbonate buffer solutions requires nursing time, cleaning time and cleansing agents for bacterial decontamination of both the bicarbonate storage tank and system loop (and/or jugs if being used), large storage rooms for storage of dry bicarbonate powder, shipping costs, and if using bicarbonate and acid jugs, potential for human injury resulting from heavy lifting.

Mixing and Delivery

Bicarbonate concentrate mixing and delivery systems typically fall into one of three categories.[18] In acute settings or in units with limited patient numbers,

bicarbonate powder is added to a jug prefilled with AAMI grade water. The jug is then physically carried to the hemodialysis station. This system, while cumbersome, allows flexibility in terms of individually customized dialysate preparation. Care must be taken after treatment to disinfect the jug using AAMI grade water mixed with sodium hypochlorite.

Larger scale systems employ large tanks with a mechanical mixing device. These types of systems allow faster turnover of dialysis patients between shifts and limit the need for spending time and labor to fill and later disinfect jugs. A large tank is prefilled with AAMI grade water to a pre-specified level and then the correct amount of bicarbonate powder is added to create the base concentrate. Bicarbonate powder should be added after the water filling cycle is complete. Bicarbonate powder can displace mixing tank water and can lead to problems with overly dilute or concentrated bicarbonate concentrate when added before or during the water fill cycle. State-of-the-art bicarbonate tanks and control units should be made of polyethylene that will help keep the work area free of rust and corrosion. The tank should be smooth and sloped at the bottom to ensure complete draining and should be equipped with alarms set to detect low amounts of bicarbonate concentrate and to detect tank overflow. The tank should also be equipped with a spray nozzle that can spread disinfectant over the entire internal surface area of the tank, should have a tight fitting, sealed lid to help reduce CO_2 loss after mixing, should have a timer to ensure adequate mixing and to avoid over-mixing, should contain sample ports to test the mixed bicarbonate solution for appropriate concentration and also to allow for testing of residual bleach during disinfection. The concentrate is then delivered to a series of dialysis machines either via gravity feed or pumping through a distribution loop.[18]

When calculating the cost of such a system, the nephrologist must take into account the one-time cost of the large tank, mechanical mixing device, and distribution loop and also any ongoing preventive maintenance costs. Other costs include that of dry sodium bicarbonate powder and the cost of shipping and storing this powder. Assuming an uptake rate of close to 2 l/h, a unit dialyzing 40 patients three times/week would require around 240 l of bicarbonate concentrate/day. Over the course of the year at a cost of 14$/100 l, this amounts to around $7300. One must also consider the nursing and HD tech time required for mixing the bicarbonate concentrate and the time required to decontaminate the tank and distribution loop.

Finally, prefilled cartridges or bags containing sodium bicarbonate attach directly to the hemodialysis machine and when mixed with AAMI grade water allow online creation of base concentrate at the point of use. Bicart and Bibag are two such cartridges that are widely used.

The Bicart cartridge, invented by Gambro, is a polypropylene container filled with sodium bicarbonate powder. The cartridge, which comes in both 720 g and 1250 g pre-filled containers, attaches to a special holder on Gambro hemodialysis machines. Use of the cartridge enables online production of a ready-to-use saturated liquid bicarbonate concentrate when mixed with water. This solution is then mixed with acid concentrate and water to produce dialysate. Use of the Bicart requires 1:1.72:42.28 (45X) proportioning.

Use of Bicart eliminates the need for daily mixing of bicarbonate concentrate, decreases the need for storage space, eliminates the need for bicarbonate jugs or a systemic loop for bicarbonate concentrate delivery, eliminates the need for systemic loop decontamination and decontamination of bicarbonate concentrate containing jugs, minimizes the risk for bacterial contamination, limits potential for injury from carrying heavy fluid containing jugs, and requires minimal work for cleanup after each treatment. Bicart preserves nursing and HD tech time for more patient focused activities.

Gambro reports that, when combined with the appropriate acid concentrate, around 200 l of dialysate with a bicarbonate concentration of 34 mmol/L can be produced from one 720 g Bicart cartridge. Via simple calculation, 571 g of sodium bicarbonate is utilized to create the liquid bicarbonate concentrate (79% efficient). The possible time for dialysate production/720 g cartridge amounts to 4 h 10 min when using a dialysate flow of 800 ml/min or to 5 h 30 min when using dialysate flow of 600 ml/min. When using the 1250 g cartridge, 300 l of dialysate with a bicarbonate concentration of 34 mmol/L can be produced. This amounts to 6 h 15 min when using dialysate flow of 800 ml/min or 8 h 20 min when using a dialysate flow of 600 ml/min.[19] It should be noted that most Indian dialysis machines are limited to dialysate flows of 500 ml/min or 800 ml/min so potential time available to dialyze while using Bicart will need to be adjusted accordingly.

In a unit where the predominant dialysate flow is 800 ml/min and the treatment time averages 4 h/treatment, the best setup seems to be one 720 g Bicart cartridge/treatment. At our institution, the negotiated price/720 g Bicart is $4.77 ($47.70/box of 10). With 20 HD chairs filled to capacity and 2 shifts/day, the cost of using the smaller Bicart cartridge amounts to $1144.80/week or $59,529.60/year. Alternatively,

if we were to dialyze the same patients with a slower dialysate flow of 600 ml/min, the 1250 g Bicart could be used for both shifts. At a cost of $7.61/cartridge, the weekly and yearly cost is considerably cheaper at $913.20 and $47,486 respectively. Both products are considerably more expensive than pre-mixing bicarbonate and delivery via a distribution loop.

The Fresenius Bibag system, is intended for use with Fresenius three-stream hemodialysis proportioning systems equipped with a Bibag module such as the modified Fresenius 2008T hemodialysis machine. The technological characteristics are similar to the Gambro Bicart in that both systems allow online preparation of a sterile bicarbonate concentrate from a single use, dry bicarbonate powder container, for use in a three-stream proportioning system using AAMI grade water. Advantages of the Bibag system are also similar to Bicart: No need for daily bicarbonate mixing, easy disposal, prevention of bacterial contamination, and small and lightweight packaging.[20]

Bicarbonate cartridges are expensive compared to conventional storage tank and loop delivery of bicarbonate concentrate, however, use of such cartridges can cut down on potential routes of infection, can limit technician time for more patient centered activities, can lead to decreased startup costs in relatively small dialysis units, and overall, simply requires less work to provide the same thing.

Bacterial Decontamination

Bicarbonate concentrate provides an excellent medium for bacterial growth. If the bicarbonate concentrate is contaminated, its combination with reverse osmosis (RO) water and acid concentrate would lead to a contaminated, proportioned dialysate that would not meet the AAMI standard for total microbial count of <200 CFU/mL and/or a total endotoxin level of <2 EU/mL.[21] In a hemodialysis unit that delivers bicarbonate to all patients from the same storage tank and delivery loop, potential problems could ensue resulting from endotoxin exposure and subsequent pro-inflammatory cytokine stimulation, especially in units where high flux dialyzers are used.[22] Additionally, inadequate decontamination and rinsing of surfaces exposed to bicarbonate (i.e., storage tank, delivery loop, jugs) can quickly lead to formation of a biofilm, deposition of carbonate and formation of disinfectant residues. These risks underscore the need for adequate cleaning, decontamination and rinsing of the bicarbonate storage tank and delivery loop (or bicarbonate jugs if using this method of bicarbonate delivery).[18]

Typical decontamination and rinsing schema for the bicarbonate containing tanks and loop require any extra bicarbonate concentrate to first be discarded. The mixing tank is filled with a pre-specified amount of AAMI grade RO water and then mixed with either sodium hypochlorite (bleach) or commercial cleansing agents such as Renalin or Minn-Care. The amount of decontamination solution must take into account the volume of the tank as well as the total volume of the delivery loop. At our institution, 40 gallons of AAMI grade water are mixed with a 0.75 gallon of bleach to create a 1.5% sodium hypochlorite cleaning solution. After a dwell time, the solution is pumped to the head tank where, through the use of a spray nozzle, the solution continuously coats the head tank internal surface for a dwell time specific to the cleansing agent before the entire solution is pumped through the bicarbonate delivery loop. At this time each patient station port is tested for the presence of sodium hypochlorite to ensure delivery of the decontamination solution throughout the delivery loop. This process is followed by a rinsing period using AAMI grade water. Each aspect of the tanks and delivery loop is rinsed and later tested to ensure no residual cleaning solution is present. The bicarbonate concentrate tanks and delivery loop must be cleaned and disinfected in this manner each week after all patients have finished their dialysis treatment. If the dialysis unit utilizes jugs for bicarbonate delivery, these jugs must be rinsed each day with AAMI grade water and cleaned once weekly with bleach followed by an AAMI water rinse and inversion to dry overnight.

An additional aspect of cleaning and disinfecting central bicarbonate delivery systems is eliminating or preventing the formation of carbonate precipitate. This is done on a weekly basis by exposing all internal surfaces of the bicarbonate concentrate tanks and delivery loop to an acetic acid or citric acid solution (acid rinse). Use of commercial agents such Renalin or Minn-care as cleansing agents eliminate the need for this step as these products contain acetic or paracetic acid. The acid rinse is carried out in a similar fashion to that of the bleach cleaning.

Units that utilize bicarbonate containing cartridges or “bags” for online production of proportioned dialysate do not require any extra decontamination or cleansing procedures as there are no bicarbonate contact surfaces available for cleaning.

Conclusion

There are many considerations to the production, mixing and delivery of the dialysate buffer. Such considerations

include the buffer contribution from the acid concentrate, the type of buffer and proportioning system used, the size of the dialysis unit and number of patients to be dialyzed, the initial costs in setting up a bicarbonate delivery loop, the method of delivery (i.e., loop, jugs or cartridge), and disinfection and decontamination procedures. The nephrologist should have a clear understanding of these aspects of dialysate buffer use in order to provide safe and effective care for dialysis patients.

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