

Comparison of intravenous sodium bicarbonate and sodium chloride combination versus intravenous sodium chloride hydration alone in reducing amphotericin B nephrotoxicity: a randomized clinical trial

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Abstract

Background and purpose: The most important adverse reaction of amphotericin B (AmB) is nephrotoxicity. The aim of this study was to assess the potential effectiveness of intravenous saline + sodium bicarbonate versus intravenous sodium chloride hydration in preventing or attenuating AmB nephrotoxicity.

Experimental approach: A randomized, non-placebo-controlled, single-blinded clinical trial was conducted in two adult hematology-oncology wards of Namazi hospital. Eligible patients were randomly assigned into either the normal saline or normal saline + sodium bicarbonate groups by the ratio of 1:2. In the normal saline group, 1000 mL of sodium chloride 0.9% (154 meq sodium) was given intravenously as two equal 500 mL volumes before and during the infusion of AmB. Patients in the saline + sodium bicarbonate group received 500 mL sodium chloride 0.9% (72 meq sodium) before and 500 mL isotonic sodium bicarbonate (72 meq sodium) intravenously during AmB infusion.

Findings/Results: The rate of AmB nephrotoxicity was comparable between normal saline and sodium bicarbonate groups (54.2% and 41.6%, respectively; $P = 0.3$). This difference did not reach the level of statistical significance after considering AmB dose and duration of the treatment. The frequency of hypokalemia and hypomagnesemia did not differ significantly between the two groups even after adjusting the results according to AmB dose and treatment duration.

Conclusion and implications: The results of the current preliminary clinical trial suggested that the combination of sodium bicarbonate and normal saline compared to normal saline alone appears to have no superiority in preventing or attenuating different studied aspects of AmB nephrotoxicity in patients with hematological malignancies.

Keywords: Amphotericin B; Sodium bicarbonate; Sodium chloride; Nephrotoxicity; Prevention.

INTRODUCTION

The most important adverse reaction of amphotericin B (AmB), a broad-spectrum antifungal agent that can significantly challenge and limit its use in clinical practice is nephrotoxicity. AmB can adversely affect both glomerular and tubular functions of the kidney

resulting in decreased glomerular filtration rate (GFR), electrolyte imbalances (e.g., hypokalemia and hypomagnesemia), distal tubular acidosis, and nephrogenic diabetes insipidus.

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Although these features are mostly transient and reversible, up to 15% of AmB nephrotoxicity cases may require renal replacement therapy (1). Nephrotoxicity was established in approximately one-third (27.5%) of the cohort in the first week of AmB treatment. Hypokalemia and renal potassium wasting was a significant finding in the study population which were attributed to nearly one-half and one-third of the AmB recipients, respectively (2,3).

During the past 4 decades, many approaches have been studied in both experimental and clinical settings to prevent or at least, mitigate AmB nephrotoxicity. These approaches have been substantially reviewed elsewhere (4-6). Among these modalities, only sodium loading before and/or during infusion of AmB and administration of lipid-based formulations of AmB (especially liposomal AmB) has been clearly demonstrated to be relatively effective and safe. However, these modalities are not devoid of drawbacks. For example, sodium loading can only prevent or alleviate AmB-induced rise in serum creatinine (Scr) or decrease in GFR rather than tubular aspects of AmB nephrotoxicity such as electrolyte abnormalities and acidosis. Regarding lipid formulations of AmB, they are generally very expensive, not easily available, and still associated with some degrees of nephrotoxicity (6).

Currently, sodium bicarbonate is indicated for the management of metabolic acidosis, hyperkalemia, and overdose of certain medications such as aspirin and tricyclic antidepressants (7). Apart from these FDA-approved labeled uses, sodium bicarbonate has been demonstrated to have nephroprotective effects in certain clinical settings including contrast-induced nephropathy and rhabdomyolysis-associated acute kidney injury (8). Regarding the former, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends either isotonic sodium chloride or sodium bicarbonate solutions for preventing contrast-induced nephropathy in high-risk patients (1A) (9). Interestingly, in a case series published in 1975, Olivero *et al.* proposed that adding bicarbonate to mannitol therapy can fully protect the kidney

from both mechanisms of renal injury by AmB including vasoconstriction and direct tubular toxicity (10).

In the current preliminary clinical trial, for the first time to the best of our knowledge, we compared the potential effectiveness of sodium bicarbonate co-administration with salt loading, as the standard of care, in preventing or attenuating different aspects of AmB nephrotoxicity.

MATERIALS AND METHODS

Type of study and study setting

This randomized, non-placebo-controlled, single-blinded clinical trial (ID: IRCT20161010030246N4) was conducted during a one-year period from early February 2018 to February 2019 in two adult hematology-oncology wards of Namazi hospital as one of the referral teaching health-care settings in south of Iran, affiliated to Shiraz University of Medical Sciences, Shiraz, I.R. Iran.

Sample size calculation

Sample size of the current study was calculated by considering $\alpha = 0.05$, 80 % power ($1-\beta = 0.8$), and data of relevant clinical studies assessing effects of different agents such as n-acetyl cysteine (11), amiloride (12), and spironolactone (13) against AmB nephrotoxicity. The sample size was calculated to be at least 30 patients.

Patient selection

Inclusion criteria were age above 15 years and receiving conventional formulation of AmB for any indication for an anticipated duration of at least 1 week. Exclusion criteria were as follows: (1) documented acute kidney injury before starting AmB defined by an increase in serum creatinine ≥ 0.3 mg/dL within 48 h, or an increase in serum creatinine by ≥ 1.5 times base line within the prior 7 days, or urine volume < 0.5 mL/kg/h for 6 h (oliguria); (2) documented chronic kidney disease before starting AmB defined as clearance creatinine below 60 mL/min/1.73 m² or history of peritoneal or hemodialysis for more than 3 months (9); (3) severe symptomatic

hypocalcemia (corrected serum calcium level below 8 mg/dL); (4) hypokalemia (serum potassium level below 3 meq/L); (5) hypomagnesemia (serum magnesium level below 1.2 mEq/L); (6) alkalosis (arterial pH above 7.5 or serum bicarbonate above 30 meq/L) (14); (7) advanced congestive heart failure (New York Heart Association, NYHA, functional class III or IV), history of receiving any systemic formulation of AmB within the recent 2 weeks; and (8) known history of hypersensitivity to sodium bicarbonate formulations.

The institutional review boards and the medical ethics committee of the hospital approved the study (Ethics No. IR.SUMS.REC.1398.460). All patients or their family members signed and approved a written informed consent form if willing to take part in the study.

Intervention

Considering the established role of sodium loading in preventing AmB nephrotoxicity, eligible patients were assigned into either the normal saline or normal saline + sodium bicarbonate groups by the ratio of 1:2 in a single-blinded manner using the simple randomization method. In the normal saline group, 1000 mL sodium chloride 0.9% (154 meq sodium) was given intravenously at a rate of 1 mL/kg/h as two equal 500 mL volumes before and during AmB infusion. Patients in the normal saline + sodium bicarbonate group received 500 mL of sodium chloride 0.9% (77 meq sodium) before and 500 mL isotonic sodium bicarbonate (77 meq sodium) at a rate of 1 mL/kg/h intravenously during AmB infusion. Isotonic sodium bicarbonate solution was prepared by adding 77 mL sodium bicarbonate 8.4% to 423 mL dextrose 5% solution. Normal saline or saline + sodium bicarbonate was continued daily during the course of AmB treatment. Any sodium depletion within AmB treatment was corrected independently.

Data gathering and study endpoints

Blood urea nitrogen (BUN) and Scr values were determined for each patient every other day during the study period. Baseline kidney

function was determined by GFR calculation through the simplified modification of diet in renal disease (MDRD) formula. The 24-h urine volume, urine creatinine, and urine as well as serum potassium and magnesium levels were determined weekly. AmB nephrotoxicity was defined by the doubling of Scr from the baseline value. Hypokalemia and hypomagnesemia were defined as serum level potassium and magnesium below 3 mEq/L and 1.2 mEq/L, respectively. Time onset of nephrotoxicity, hypokalemia, and hypomagnesemia after initiation of AmB was also determined. Any probable approach to managing AmB nephrotoxicities such as daily dose reduction, early discontinuation, or renal replacement therapy was recorded.

Regarding sodium bicarbonate safety, mental status, serum levels of sodium, potassium, magnesium, and calcium, relevant signs/symptoms of hypocalcemia, hypokalemia, and hypomagnesemia, arterial blood gas, and electrocardiogram were monitored daily during the study period in the saline + sodium bicarbonate group.

Statistical analyses

Per protocol analysis was exploited to analyze data of all individuals who completed the study. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Normally- and non-normally distributed continuous data were expressed as mean \pm standard deviation and median (interquartile range), respectively. Categorical variables were reported as percentages. Chi-square or Fisher exact test (if $> 20\%$ of the categories has expected frequencies < 5) were exploited to evaluate possible associations among categorical variables. Parametric and non-parametric continuous variables were analyzed by the independent t and Mann-Whitney tests, respectively. Multivariate logistic regression analysis was employed to adjust our intervention for probable confounding factors including AmB dose and duration of treatment. Comparison of the mean values of Scr and GFR at different time points during AmB treatment within and between saline versus saline + bicarbonate groups was performed by the one-

way analysis of variance (ANOVA) with repeated measures. *P*-values < 0.05 were considered as statistical significance. All the above statistical analyses were carried out by the SPSS (Statistical Package for the Social Sciences) version 18 software.

RESULTS

During the study period, 40 patients met the inclusion/exclusion criteria. Among them, 5 were transferred to another ward and 2 individuals died before complementing the 1-week AmB treatment. The remaining 33 subjects were randomly assigned into either normal saline or saline + sodium bicarbonate group with a ratio of 1:2. In other words, 11 and 22 patients were given normal saline and normal saline + sodium bicarbonate, respectively. Two patients in the treatment group refused to continue the study. Therefore, an overall 31 subjects including 20 in the saline

+ sodium bicarbonate group and 11 in the normal saline group completed the clinical trial (Fig. 1).

Regarding gender, 19 (61.3%) and 12 (38.7%) individuals were male and female, respectively. The mean \pm SD age of the cohort was 38.8 ± 13.5 years. The underlying hematologic malignancies of the study population were acute lymphoid leukemia (70.96%), acute myeloid leukemia (25.8%), and multiple myeloma (3.2%). Different demographic as well as baseline clinical, and paraclinical characteristics of the study population including age, sex, diagnosis, AmB dose and treatment duration, co-administration of nephrotoxic medications (e.g., vancomycin, aminoglycosides, acyclovir, and furosemide), BUN, serum creatinine, potassium, magnesium, and GFR were comparable between two groups (Table 1). None of the studied patients received cyclosporine, cisplatin, and ifosfamide.

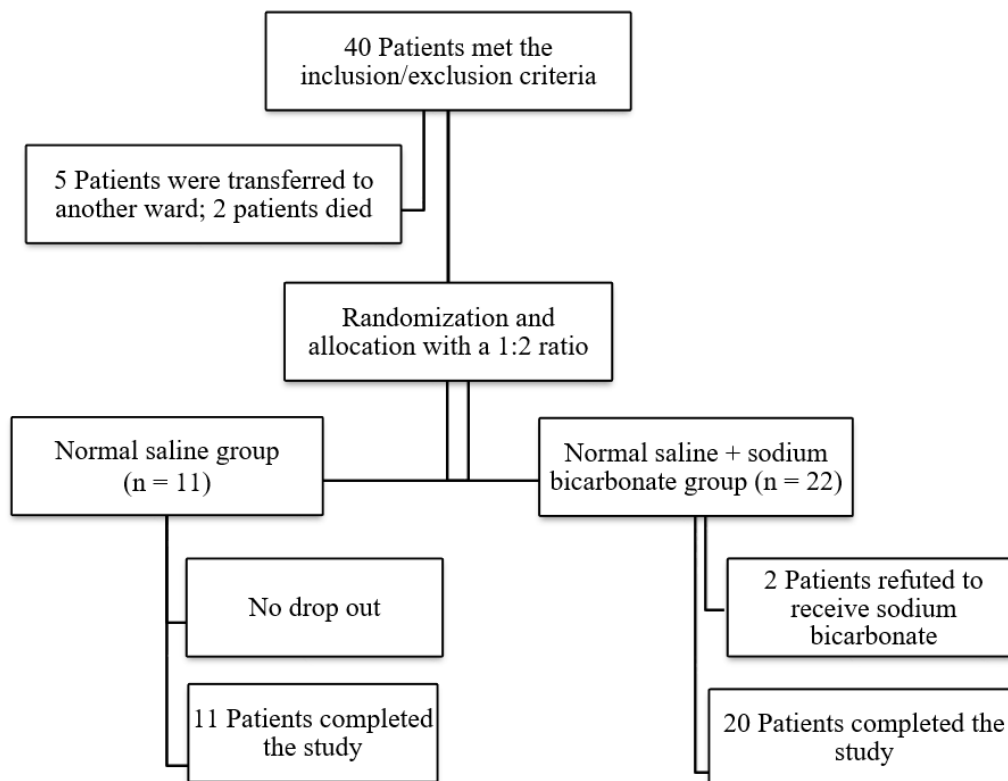


Fig. 1. Consort flowchart of the study

Table 1. Comparison of demographic and baseline paraclinical characteristics of the study population in normal saline and sodium bicarbonate groups (n = 31).

Characteristics	Groups		P-value
	Normal saline (n = 11)	Normal saline + sodium bicarbonate (n = 20)	
Sex, male/female	9/2	11/9	0.190
Age, mean ± SD (years)	40.27 ± 13.25	37.35 ± 14.71	0.588
Weight, mean ± SD (kg)	61.17 ± 7.87	69.60 ± 11.54	0.670
Acute lymphoblastic leukemia	8 (72.73%)	14 (70%)	0.894
Acute myeloblastic leukemia	3 (27.27%)	5 (25%)	0.887
Multiple myeloma	0	1 (5%)	0.645
Duration of amphotericin B treatment, mean ± SD (days)	15.09 ± 11.31	15.65 ± 6.75	0.864
Amphotericin B dose, mean ± SD (mg)	47.72 ± 17.04	43.99 ± 13.82	0.513
Co-administration of vancomycin (%)	6 (54.55)	13 (65)	0.211
Co-administration of aminoglycosides (%)	1 (9.09)	2 (10)	0.896
Co-administration of acyclovir (%)	10 (90.91)	11 (55)	0.902
Co-administration of loop diuretics (%)	2 (18.18)	3 (15)	0.899
Serum creatinine, mean ± SD (mg/dL)	0.86 ± 0.26	0.92 ± 0.32	0.621
Blood urea nitrogen, mean ± SD (mg/dL)	15.30 ± 5.31	15.52 – 6.34	0.924
Glomerular filtration rate, mean ± SD (mL/min/1.73 m ²)	99.23 ± 38.28	110.12 ± 32.79	0.411
Serum potassium, mean ± SD (mEq/L)	3.86 ± 0.52	3.82 ± 0.74	0.862
Serum magnesium, mean ± SD (mEq/L)	2.01 ± 0.82	4.9 ± 0.57	0.733

Table 2. Comparison of paraclinical characteristics of the study population during amphotericin B treatment in normal saline and sodium bicarbonate groups (n = 31)

Characteristics	Groups		P-value	
	Normal saline (n = 11)	Normal saline + sodium bicarbonate (n = 20)	Univariate	Multivariate
Serum creatinine, range (mg/dL)	0.3-2.1	0.2-2.6	0.658	0.225
Blood urea nitrogen, range (mg/dL)	6-57	5-56	0.980	0.655
Serum potassium, range (mEq/L)	2.2-4.8	1.2-5.3	0.125	0.337
Serum magnesium, range (mEq/L)	1.3-3.8	1-2.1	0.052	0.270
Urine creatinine, range (mg/dL)	167-1300	94.5-11642	0.19	0.35
Urine volume, range (L)	1000-4700	500-4600	0.76	0.912
Urine potassium, range (mEq/L)	15-49	11-49	0.41	0.261
Urine magnesium, range (mEq/L)	2.1-1160	13-391	0.06	0.27

After adjusting groups for probable confounding factors (e.g. AmB dose and treatment duration), studied aspects of AmB nephrotoxicity including serum creatinine, potassium, and magnesium as well as 24-h urine volume, urine creatinine, potassium, and magnesium did not differ significantly between the two groups (Table 2).

The time course of changes in the mean value of Scr at different time points during the study was demonstrated in Fig. 2. The mean change of Scr within each group was statistically significant ($P = 0.024$). However, this change did not differ significantly between the two study groups.

According to the aforementioned definition, 15 patients (48.4%) developed nephrotoxicity within the course of AmB treatment. Based on univariate analysis, the rate of AmB nephrotoxicity was comparable between normal saline and normal saline + sodium bicarbonate groups (54.2% and 41.6%, respectively; $P = 0.3$). This difference did not reach the level of statistical significance after considering AmB dose and duration of treatment. The median time onset of AmB nephrotoxicity in normal saline (3.7 days) and normal saline + sodium bicarbonate (4.5 days) groups were not also statistically significant.

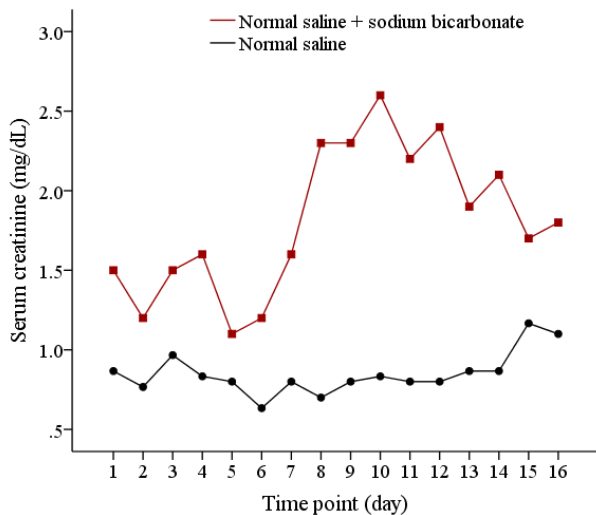


Fig. 2. The changing pattern of serum creatinine at different time points in normal saline and normal saline + bicarbonate recipients. Data present the mean \pm SD.

During AmB treatment, 71.5% and 23.8% of patients developed hypokalemia and hypomagnesemia, respectively. The frequency of hypokalemia and hypomagnesemia did not differ significantly between the two groups even after adjusting results according to AmB dose and treatment duration. The mean \pm SD time onset of hypokalemia and hypomagnesemia (6.8 ± 2.1 and 8.2 ± 3.5 days, respectively) was also comparable between normal saline and normal saline + sodium bicarbonate groups.

None of the patients in neither group required early discontinuation of AmB or renal replacement therapy for the management of AmB nephrotoxicity. The mean \pm SD duration of ward stay did not differ significantly ($P = 0.72$) between normal saline (47.5 ± 26.3 days) and saline + sodium bicarbonate groups (51.6 ± 28.4 days). The mortality rate was also comparable between the two groups.

No case of symptomatic hypokalemia, hypomagnesemia, hypocalcemia, hypernatremia, and metabolic alkalosis was observed in the saline + sodium bicarbonate group during the study.

DISCUSSION

According to the fact that AmB exerts its nephrotoxicity *via* different pathways, exploring the potential benefits of multi-

functional nephroprotective agents seems rational. In this regards for example, in a double-blinded, placebo-controlled, multicenter clinical trial, Karimzadeh *et al.* demonstrated that co-administration of 600 mg n-acetyl cysteine, a cysteine pro-drug with antioxidant, anti-apoptotic, and vasodilatory effects, twice a day was significantly associated with preventing AmB nephrotoxicity or decreasing estimated creatinine clearance caused by AmB (11). However, the same study group failed to demonstrate any beneficial effects of the same regimen of oral n-acetyl cysteine in preventing or ameliorating electrolyte imbalances caused by AmB including hypokalemia, hypomagnesemia, and renal potassium as well as magnesium wasting syndrome (15).

Although the only relevant prospective, double-blind, controlled clinical trial failed to show the effectiveness of mannitol in diminishing AmB nephrotoxicity (16), some data in the literature suggested that combined use of mannitol with sodium bicarbonate might be clinically effective in preventing nephrotoxicity of AmB (5-10). In this preliminary clinical trial, the beneficial effects of sodium bicarbonate co-administration against major features of AmB nephrotoxicity were compared to isotonic saline loading as the established and commonly-used approach in this area.

Lack of sodium bicarbonate beneficial effects in preventing or attenuating AmB nephrotoxicity in the current clinical trial are in line with data from most other clinical settings such as cardiac surgery-associated acute kidney injury. In a systematic review and meta-analysis of 5 relevant randomized controlled trials by Tie *et al.* sodium bicarbonate compared with placebo was not associated with a reduced incidence of acute kidney injury (relative risk (RR) = 0.99; 95% confidence interval (CI) = 0.78 to 1.24; $P = 0.911$), renal replacement therapy (RR = 0.94; 95% CI = 0.49 to 1.82; $P = 0.861$), and hospital mortality (RR = 1.37; 95% CI = 0.46 to 4.13; $P = 0.572$). Even worse, sodium bicarbonate administration significantly prolonged the duration of mechanical ventilation as well as ICU length of stay and increased incidence of alkalemia (17).

Similar findings were identified in another meta-analysis published one year later (18). The results of at least one experimental investigation in rats reported that pre-treatment with 0.28 meq/L sodium bicarbonate added to drinking water for 7 days did not prevent studied indexes of cyclosporine-induced nephrotoxicity including decreased creatinine clearance and increased urinary N-acetyl- β -D-glucosaminidase (19).

The nephroprotective functions of sodium bicarbonate have been only demonstrated in contrast-induced nephropathy and rhabdomyolysis. The suggested mechanisms of sodium bicarbonate in preventing contrast-induced nephropathy include (1) volume expansion that may suppress vasopressin and renin-angiotensin; (2) blocking the production of free radicals mediated by the Haber-Weiss reaction secondary to increasing tubular PH; (3) scavenging potent peroxy nitrate *via* nitric oxide-mediated pathways (20). However, considering the potential adverse effects and possibility of error in preparing isotonic sodium bicarbonate solution either at the bedside or in the hospital pharmacy service, the 2012 KDIGO guideline does not prefer sodium bicarbonate solution over normal saline for preventing contrast-induced nephropathy in high-risk patients (9).

The issue appears to be somewhat more complex in the setting of rhabdomyolysis-associated acute kidney injury. There is no head-to-head controlled clinical study comparing isotonic saline alone with the combination of isotonic saline and sodium bicarbonate solution. The only data in favor of sodium bicarbonate beneficial effects are derived from uncontrolled case series in severe rhabdomyolysis. It has been hypothesized that urine alkalization can block the formation of ferrihemate (hematin), a potent toxic agent against proximal tubular cells, by preventing the release of free iron from myoglobin. Sodium bicarbonate can also potentially inhibit the production of F2-isoprostane with vasoconstricting properties and precipitation of uric acid in tubules (21). Although not determined and beyond the scope of our study, but according to current results it can be

inferred that sodium bicarbonate may exert its protective effects against AmB nephrotoxicity mainly through inhibition of tubule-glomerular feedback and appears to have no additional mechanism compared to isotonic saline.

The main drawback of sodium bicarbonate administration even in cases of proven efficacy is lack of consensus regarding the optimal time to its initiation, the volume of solution, and duration of treatment. In contrast-induced nephropathy, for example, the 2012 KDIGO guideline has been suggested that 154 meq isotonic sodium bicarbonate should be administered intravenously at a rate of 1-1.5 mL/kg/h for 3-12 h before and 6-12 h after contrast-media exposure (9). To prevent rhabdomyolysis-associated acute kidney injury, about 130 meq/L sodium bicarbonate should be started as soon as possible, preferably within the first 6 h of muscle injury at an initial rate of 200 mL/h, adjusted to achieve urine pH above 6.5 or urine output of 300 mL/h or more for at least the first 24 h (21). The sodium bicarbonate regimen exploited in this clinical trial was relatively similar to those used commonly in clinical practice. However, neither urine output nor pH was considered as targets of bicarbonate administration in our cohort.

Apart from clinical efficacy, the safety of sodium bicarbonate administration is also a major concern. Sodium bicarbonate administration can result in over-alkalinization and a paradoxical transient intracellular acidosis. The latter can especially occur in patients with severe acidaemia. Shift to the left in the oxygen-hemoglobin dissociation curve secondary to an increase in hemoglobin affinity for oxygen can be observed. This can decrease oxygen delivery to tissues and potentially increase lactic acid production and accumulation (22,23). Other complications of sodium bicarbonate administration are hypernatremia, hypokalemia, a decrease in the level of ionized calcium, hyperosmolality, volume overload, hypoventilation, cardiac arrhythmia, and injection-site reactions (e.g., extravasation) (24). Therefore, mental status, serum levels of sodium as well as potassium, arterial blood gas, and electrocardiogram should be monitored (22). Probable physical and/or chemical incompatibilities of sodium

bicarbonate with other co-administered medications such as calcium salts, ciprofloxacin, dobutamine, and dopamine should also be taken into account (25). In our study, the sodium bicarbonate regimen in the saline + sodium bicarbonate recipients was well tolerated without any symptomatic case of hypokalemia, hypomagnesemia, hypocalcemia, hypernatremia, and metabolic alkalosis.

The major drawbacks of the current study were relatively small sample size and the likelihood of statistical underpowering (calculated statistical power of the study was 73.07%) partially because of considering numerous inclusion/exclusion criteria and designing the study as a non-placebo-controlled, and single-blinded one. The last issue may be due to the fact that it was not feasible for the researchers to make the same package of intravenous administration for both normal saline and saline + sodium bicarbonate, secondary to lack of available clean rooms for preparing intravenous medications. Therefore, the nursing staff in charge of patient medication administration were not blinded regarding the study groups.

CONCLUSION

The results of the current preliminary clinical trial suggested that the combination of sodium bicarbonate and normal saline compared to normal saline alone appears to have no superiority in preventing or attenuating different studied aspects of AmB nephrotoxicity (including a decrease in GFR, increase in Scr, urine 24-h volume, and electrolyte imbalances) in patients with hematological malignancies. More clinical trials with large sample size and better methodology (placebo-controlled and double-blinded) may be warranted in this field.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest in this study.

AUTHORS' CONTRIBUTION

I. Karimzadeh contributed to data analysis and manuscript reviewing. A. Sepehr-Sobhani contributed to patient selection, implementing the interventions, and data gathering. M.J. Khoshnoud contributed to the study design, data analysis, and manuscript review. M.M. Sagheb contributed to study design, patient selection, and clinical interpretation of data. R. Vejdani contributed to study design, patient selection, and clinical interpretation of data. A. Jalali contributed to data analysis and manuscript drafting. M. Mahi-Birjand contributed to data analysis and manuscript drafting. All authors have read and approved the final version of the manuscript before submission.

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