Efficacy and Safety of Sodium Benzoate in The Management of Hyperammonemia in Decompensated Chronic Liver Disease of the Childhood—A Double-blind Randomized Controlled Trial

Pandey Snehavardhan, Bikrant B. Lal, Vikrant Sood, Rajeev Khanna, and Seema Alam

See ''Bye Bye Benzoate: What Next for Hyperammonemia in Liver Disease?'' by Henkel and McKiernan on page 158.

ABSTRACT

Objective: The objective was to evaluate the efficacy and safety of sodium benzoate in the management of hyperammonemia and hepatic encephalopathy (HE) in decompensated chronic liver disease.

Methods: It was a prospective, interventional, double-blinded randomized controlled trial conducted from August 2017 to December 2018. Children with decompensated chronic liver disease and hyperammonemia were included in the study. Those with ammonia >400 μg/dL, already receiving sodium benzoate or with grade III ascites were excluded. Group A received sodium benzoate (400 mg/kg loading dose followed by 200 $mg \cdot kg^{-1} \cdot day^{-1}$maintenance for 5 days) along with the standard medical therapy. Group B received standard medical therapy with placebo.

Results: A total of 108 episodes of hyperammonemia occurred in 86 patients of whom 16 were excluded. The final analysis included 46 episodes in each group. The median decrease in ammonia from baseline to day 5 was 52 μg/dL in group A versus 42 μg/dL in group B ($P = 0.321$). There was a significant decrease in ammonia on days 1 and 2 in group A as compared to group B, but not on subsequent days. There was no significant difference in the resolution of HE (57.1% vs 50%; $P = 1$), but there was higher, albeit insignificant increase in ascites in group A (15.9% vs 4.5%).

Conclusions: Addition of sodium benzoate significantly reduced the ammonia levels on the first 2 days of therapy but the effect was not sustained till day 5. The effect of sodium benzoate would probably be more sustained, if higher dosage (400 $mg \cdot kg^{-1} \cdot day^{-1}$) could be used under monitoring of benzoate levels. There was no effect on resolution of HE. Sodium benzoate caused an increasing trend of adverse events with no effect on short-term survival.

Key Words: children, encephalopathy, hyperammonemia, sodium benzoate

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What Is Known

- Lactulose and rifaximin are the first-line drugs for the treatment of hepatic encephalopathy.
- Sodium benzoate is used to treat encephalopathy in urea cycle defects.

What Is New

- Sodium benzoate transiently decreases ammonia without sustained effect.
- This effect does not translate to improvement in hepatic encephalopathy.

Hepatic encephalopathy (HE) is one among the most devastating complications in children with chronic liver disease (CLD) (1,2). Diagnosis of HE is, however, often difficult, especially in younger children leading to delayed diagnosis and delay in initiation of specific therapy (3,4). Recently, it has been shown that as many as 50% to 57% of children with CLD suffer from minimal HE, and these children have elevated ammonia levels (5,6). Among the various pathogenesis for HE, the case for ammonia is most compelling with precipitation of HE by factors that elevate ammonia, and resolution/ improvement of HE by anti-ammonia therapy (7,8). Hyperammonemia (HA) is a major contributory factor for HE in cirrhosis owing to several factors: presence of portosystemic shunts leading to decreased first pass clearance, low muscle mass in cirrhotics leading to decreased alternate ammonia clearance, increased glutaminase activity in cirrhotics, and use of diuretics leading to metabolic alkalosis further contributing to HA (9,10). In recent studies, ammonia levels have

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From the Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India.

Address correspondence and reprint requests to Seema Alam, MD, Professor and Head, Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, New Delhi 110070, India (e-mail: seema_alam@hotmail.com).

Compliance with ethical requirements: Ethical approval was obtained from the institutional ethical committee (IEC/2017/48/NA03). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This was a prospective interventional double-blinded randomized control trial registered with Clinical Trials Registry of India (CTRI/2017/08/009329).

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www.clinicaltrials.gov registration number: CTRI/2017/08/009329.

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been shown to correlate with grades of HE in cirrhotic adults and higher ammonia levels predicted poor outcome (11,12). The metabolism and toxicity of ammonia has been studied extensively in many in vitro and in vivo models with an ultimate goal to find better ways to lower ammonia (13). Nonabsorbable disaccharides such as lactulose and antibiotics such as rifaximin decrease the production of ammonia and are the first-line therapy for HA in liver diseases (14). Other drugs that increase ammonia excretion such as sodium benzoate, phenyl acetate, and branched-chain amino acids have been widely used in lowering ammonia due to urea cycle defects but less commonly in CLD. Sodium benzoate is an FDA-approved food preservative commonly used in children with urea cycle defects in parenteral and oral forms. Sodium benzoate has been found to be as effective as lactulose to decrease ammonia in patients with cirrhosis and portosystemic shunts (15–18). Its additive effect with lactulose and other anti-ammonia measures has, however, not been studied. Sodium benzoate is an effective ammonia scavenger, although questions have been raised over its utility in CLD due to its significant sodium load (17). Because assessment of changes in grades of encephalopathy is difficult in small children, and all therapies target ammonia specifically, we evaluated the effect of adding sodium benzoate to standard medical therapy (SMT) on decreasing ammonia, which would be a more objective evidence of its efficacy. Our primary objective was the efficacy of sodium benzoate in lowering ammonia in decompensated CLD of childhood. Our secondary objective was to assess the efficacy of adding sodium benzoate to SMT in resolution of HE by day 5.

PATIENTS AND METHODS

The study was conducted in the department of Pediatric Hepatology at the Institute of Liver and Biliary Sciences, New Delhi, India from August 2017 to December 2018. The study was approved by the institutional ethics committee and enrolled with Clinical Trials Registry India (CTRI/2017/08/009329). Written informed consent was obtained from the parents of each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional ethics committee. Ammonia levels were measured for all children with CLD up to age of 18 years admitted with suspected encephalopathy. Those with HA defined as ammonia levels >150 μg/dL for infants and 100 μg/dL for older children were included in the study (19). Exclusion criteria were arterial ammonia >400 μg/dL, sodium benzoate received within a week before enrollment, those on renal replacement therapy or plasmapheresis and presence of grade III ascites (as per International Ascites Club classification) (20).

CLD was diagnosed on the basis of the presence of fibrosis or cirrhosis on liver biopsy and/or ultrasonography findings with evidence of portal hypertension demonstrated on endoscopy. The etiology of the underlying CLD was as per standard diagnostic criteria. Presence of decompensation was defined as the presence of one or more of jaundice, ascites, variceal bleed, or HE. HE was graded using the Modified West Haven criteria (21) for children older than 3 years and the scale for ''Assessment of Encephalopathy in Young Children'' as described by the Pediatric Acute Liver Failure study group for children younger than 3 years (3).

The study was a double-blind, placebo-controlled, randomized controlled trial. Computerized block randomization with a block size of 10 was used to randomly allocate each patient to either group A receiving sodium benzoate along with the SMT or group B who received placebo along with SMT. A nondepartmental colleague generated the random allocation sequence and the allocation concealment was ensured by using sealed opaque envelopes. Both the investigator and the patients were blinded. Two set of drug packets were prepared in the departmental laboratory. Group A received drug packets containing 2 g sodium benzoate and 2 g of powdered sugar, whereas group B received 4 g packets of powdered sugar as placebo. The drug packets were prepared in the departmental laboratory with the help of a pharmacist on a standardized digital weighing machine to ensure precision and accuracy of its contents. Each packet of 2 g was then dissolved in 20 mL of 10% dextrose and the exact dose was aspirated using a syringe and administered to the patient perorally or through a nasogastric tube. The dose of drug used was 400 mg/kg as a bolus dose followed by $200\,mg \cdot kg^{-1} \cdot day^{-1}$ for next 5 days. The daily dose was given in 4 divided doses. All enrolled patients received SMT which included lactulose (started at 0.5 mL/kg/dose 4 times a day and titrated based on number and consistency of stools), rifaximin (20 mg/kg/dose), which is the centre's protocol for management of suspected HE. Adequate protein (1.5 g/kg) and calorie intake, fat-soluble vitamin, and micronutrient supplementation were given to all patients. Appropriate antibiotics as per institutional protocol were used. As per this protocol, children with grade 1 ascites were monitored whereas those with grade 2 ascites were treated with salt restriction and diuretics.

The primary outcome measure was the change in the blood ammonia levels after 5 days of therapy. Secondary outcome measures included change in ammonia on each day till day 5, resolution of HE by day 5, development/increase in ascites, changes in serum sodium, length of hospital stay, adverse events, and survival with native liver (SNL) at days 28 and 90. The patients' clinical and laboratory details were filled in a pretested pro forma for each patient. The patient was monitored for HE, ascites, and electrolyte imbalance. Resolution of HE was defined as no overt HE on day 5 in those having overt HE at the time of enrollment. The ascites was monitored by clinical examination, ultrasound, and serial monitoring of weight and abdominal girth. ''Increasing ascites'' was defined on the basis of ultrasound. Arterial blood samples were sent for the measurement of ammonia in an ice box and processed ensuring standard procedure. Arterial blood gas and electrolytes were monitored daily for 5 days from the date of enrolment. The duration of hospital stay was calculated from the date of enrollment to the date of discharge. The final outcome was recorded on days 28 and 90 as SNL, death, or liver transplantation. If serum sodium levels increased above 155 mEq/L or ammonia >400 μg/dL or there was increasing ascites not responding to diuretics, then the subject was excluded from the study population and considered as treatment failure. All such excluded patients were treated as per recommendations.

STATISTICAL ANALYSIS

The sample size was calculated as 35 in each group to detect a difference in ammonia levels with a type 1 error of 0.05 and a power of 0.8. On the basis of a previously published study, where the difference within each group was normally distributed with a standard deviation of 56, the true difference in the means of the experimental and control group was 25% in former (16). Considering 15% as the dropout rate, the number of patients in each group would be 42. Continuous variables in a normal distribution were expressed as mean ± standard deviation and the categorical variables were expressed as proportions. The continuous variables were compared using Student *t* test for data with normal distribution or Mann-Whitney *U* test for data with non-normal distribution, whereas the categorical variables were compared between using Chi square or Fisher Exact test. Any difference with effect size showing *P* value of <0.05 was said to statistically significant. Per protocol analysis was done. Statistical analyses were performed using SPSS version 22.0 (RBM Corp Ltd, Armonk, NY).

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RESULTS

During the study period there were 108 episodes of HA in 86 patients. Sixteen episodes of HA were, however, excluded (3 had grade III ascites, 7 had received sodium benzoate within 1 week before enrollment, 2 patients had baseline ammonia >400 μg/dL, and another 4 did not consent for the study). Ninety-two episodes of HA were randomized such that each group had 46 episodes. Two episodes of HA each were excluded from groups A and B due to plasma exchange and deterioration in clinical status, respectively. Hence, 44 episodes of HA in each group were analyzed at the end of the study period on per-protocol analysis (Fig. 1). Table 1 shows the baseline demographic, clinical, and laboratory data of the 2 groups.

Changes in Serum Ammonia and Hepatic Encephalopathy

Using the Mann-Whitney *U* test for a cohort with non-normal distribution, the change in ammonia from days 0 to 5 was not statistically different between the 2 groups after 5 days of the intervention, $P = 0.321$ (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B734*). On daily comparison of the ammonia between the 2 study groups, there was a significant decrease in ammonia on days 1 and 2 in group A as compared to group B. From day 3 onwards, the decrease in ammonia was, however, not significantly different in the 2 groups (Fig. 2). Within group A there was a significant decrease in ammonia levels between days 0 and 5, whereas in the group B the decrease in ammonia levels as compared to baseline was significant on days 3 and 4 only (Supplemental Fig. 1, Supplemental Digital Content, *http://links.lww.com/MPG/B734*). There were 21 patients in group A and 26 patients in group B with definite overt HE at the beginning of the study. There was no significant difference in the resolution of overt HE in between the groups after 5 days of the intervention (57.1% vs 50%; odds ratio 0.89; 95% confidence interval [CI] 0.35–2.26; $P = 1$).

Adverse Effects

Increase in ascites was seen in 15.9% of those receiving sodium benzoate versus 4.5% of those receiving placebo. This difference was not statistically significant though. The other adverse events were comparable between the 2 groups: nausea (36.4% vs 22.7%), vomiting (31.8% vs 22.7%), headache (13.6% vs 0), tinnitus (6.8% vs 0), and vertigo (6.8% vs 0) (Table 2). No patient in either group developed hypernatremia (serum sodium >145 mEq/L). The rise in serum sodium by day 5 was not significantly different in the 2 groups (2.1 ± 3.9 vs 1.4 ± 4.0 mEq/L; man difference 0.61, 95% CI: −1.1–2.31; $P = 0.473$). No patient required discontinuation of therapy due to adverse events.

Effect of Sodium Benzoate on Outcome

There was no significant difference in the mean duration of hospital stay (11.8 ± 9.52 vs 9.95 ± 7.6 days, $P = 0.315$) and in the

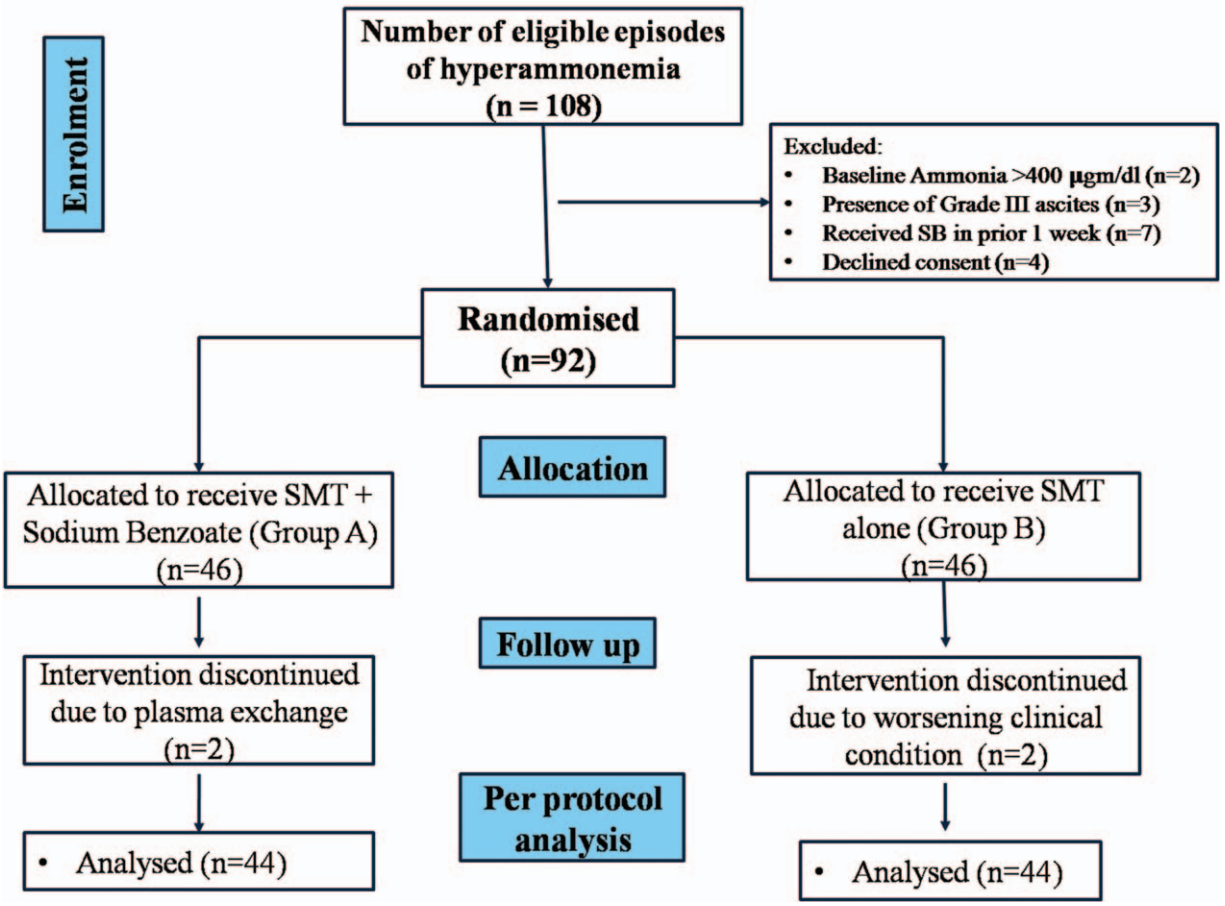

FIGURE 1. CONSORT diagram for patient selection, randomization, allocation, follow-up, and analysis. SMT = standard medical therapy.

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TABLE 1. Baseline demographic, clinical, and laboratory data in the 2 study groups

Variable	Group A (n = 44)	Group B (n = 44)	Effect size (95% CI)	P
Age, mo	61.7 ± 64.9	73.9 ± 70.8	−12.21 (−41.02–16.5)	0.402
Gender: Boys (n)	33 (75%)	32 (72.7%)	1.1 (0.43–2.91)	1.0
Jaundice (n)	41 (93.2%)	38 (86.4%)	2.15 (0.5–9.2)	0.48
Ascites (n)	29 (65.9%)	29 (65.9%)	1 (0.41–2.41)	1.0
Overt hepatic encephalopathy (n)	21 (47.7%)	26 (59.1%)	0.632 (0.27–1.46)	0.393
Etiology				
Biliary atresia (n)	12 (27.3%)	16 (36.4%)	0.65 (0.26–1.62)	0.493
Other CCLD (n)	13 (29.6%)	7 (15.9%)	2.2 (0.78–6.2)	0.493
AILD (n)	7 (15.9%)	10 (22.8%)	0.64 (0.22–1.88)	0.59
Wilson disease (n)	4 (9.1%)	7 (15.9%)	0.52 (0.14–1.9)	0.52
Chronic hepatitis B (n)	3 (6.8%)	3 (6.8%)	1 (0.1–5.2)	1.0
Metabolic liver disease (n)	2 (4.5%)	1 (2.2%)	2.04 (0.17–23.4)	1.0
Cryptogenic (n)	3 (6.8%)	nil	N/A	0.24
Hemoglobin, g/dL	9.5 ± 1.75	9.1 ± 1.8	0.45 (0.3–1.2)	0.238
White blood cells, cells/mm^3	15.7 ± 7.34	14.5 ± 9.6	1.19 (−2.4–4.83)	0.515
Platelet count, $10^9/mm^3$	204.8 ± 137.1	184 ± 121	20.8 (−34.1–75.72)	0.453
Blood ammonia, μg/dL	181.77 ± 47.59	186.3 ± 55.8	−4.56 (−26.5–17.4)	0.68
Total serum bilirubin, mg/dL	15.6 ± 9.5	19.5 ± 14.2	−3.94 (−9.07–1.18)	0.13
Serum albumin, g/dL	2.3 ± 0.6	2.4 ± 0.6	−0.11 (−0.38–1.53)	0.40
INR	1.9 ± 0.8	2.1 ± 1.2	−0.12 (−0.58–0.32)	0.57
Blood urea, mg/dL	25.6 ± 18.7	25.08 ± 18.1	0.527 (−7.2–8.3)	0.89
Serum creatinine, mg/dL	0.3 ± 0.29	0.28 ± 0.21	0.019 (−0.08–0.128)	0.72
Serum sodium, mEq/L	132.9 ± 4.9	134.2 ± 3.15	−1.27 (−3.01–0.47)	0.15
Serum potassium, mEq/L	3.9 ± 0.79	4.04 ± 0.63	−0.04 (−0.35–0.25)	0.75
PELD score	23.48 ± 10.11	23.75 ± 10.3	−0.273 (−4.61 to −4.072)	0.901

AILD = autoimmune liver disease; CCLD = chronic cholestatic liver disease; 95% CI = 95% confidence interval; INR = international normalized ratio; PELD = pediatric end-stage liver disease.

SNL at day 28 (79.3% vs 78.9%; $P = 0.97$) and day 90 (51.7% vs 52.6%; $P = 0.94$) in groups A and B, respectively. In group A, 28.6% died awaiting LT and 19.7% underwent LT.

DISCUSSION

The addition of sodium benzoate to SMT led to an early but transient decrease in ammonia as compared to SMT alone but this did not translate to improved resolution of HE. Sodium benzoate was well tolerated in all children without increase in adverse events as compared to placebo. There have been 2 randomized controlled studies evaluating the efficacy of sodium benzoate versus lactulose in cirrhotic adults, where sodium benzoate was found to be as effective as lactulose in lowering ammonia (15,18). In another crossover study in cirrhotic adults comparing sodium benzoate with sodium phenylacetate, sodium benzoate led to greater reduction of ammonia and improvement in HE scores as compared to sodium phenylacetate (16). None of the studies have, however, studied the effect of adding sodium benzoate to lactulose. Lactulose and rifaximin are the recommended first-line anti-ammonia measures (14). In the present study, we evaluated if adding sodium benzoate to currently accepted SMT provided additional benefit. Even though there was no significant difference in reduction in ammonia on day 5, there was a significantly rapid decline in ammonia on first 2 days in the sodium benzoate arm. Failure to sustain this response up to day 5, however, makes us believe this could likely be because we used a much higher dose of 400 mg/kg as loading dose on day 0 followed by maintenance dose of 200 $mg \cdot kg^{-1} \cdot day^{-1}$ thereafter. Within the groups, there was a significant decrease in ammonia on all days up to day 5 as compared to baseline (except on day 4) in group A but in group B, there was decrease only on days 3 and 4 as compared to baseline. Hence, unlike HA due to urea cycle defects, sodium benzoate did not show an additional advantage in lowering ammonia in patients with decompensated CLD. The reason for this is probably related to the pharmacokinetic properties of the drug in these different diseases. Sodium benzoate is first conjugated by coenzyme A forming benzoyl CoA, which then conjugates with glycine in liver and kidney mitochondria forming hippurate which is rapidly excreted by the kidneys via glomerular filtration and tubular secretion (22). In patients with decompensated CLD, the enzymes necessary for the conjugation reactions may be severely limited leading to sodium benzoate's suboptimal effect. The significantly greater reduction in ammonia on first 2 days after receiving a bolus of 400 mg/kg possibly raises the question whether higher doses of sodium benzoate is required to lower ammonia in children. The ammonia-lowering effect would have been probably more sustained, if we could use higher dosage (400 $mg \cdot kg^{-1} \cdot day^{-1}$) of sodium benzoate while monitoring the benzoate levels. The rapid reduction with bolus dose also raises the possibility that this drug could possibly be used to rapidly lower ammonia in patients with acute liver failure to lower the intracranial pressure and cerebral edema that is detrimental in these patients. The sodium load would probably also contribute to the therapeutic hyperosmolarity that is desirable in this group of patients. The safety and efficacy in acute liver failure, however, needs to be further studied to prove these hypotheses.

Only 51.1% of the children with suspected HE and HA had definite clinical features of overt HE. This could be due to a significant number of young children in the cohort (47.7% of the children in the study were younger than 3 years of age). Among those with definite overt HE, resolution of HE was similar between the 2 groups (group A: 57.1% vs group B: 50%; odds ratio 0.89; 95% CI 0.35–2.26; $P = 1$). Similarly, in the study by Sushma et al (15), 80% patients showed improvement in HE with sodium benzoate, whereas 77% showed improvement with lactulose. The

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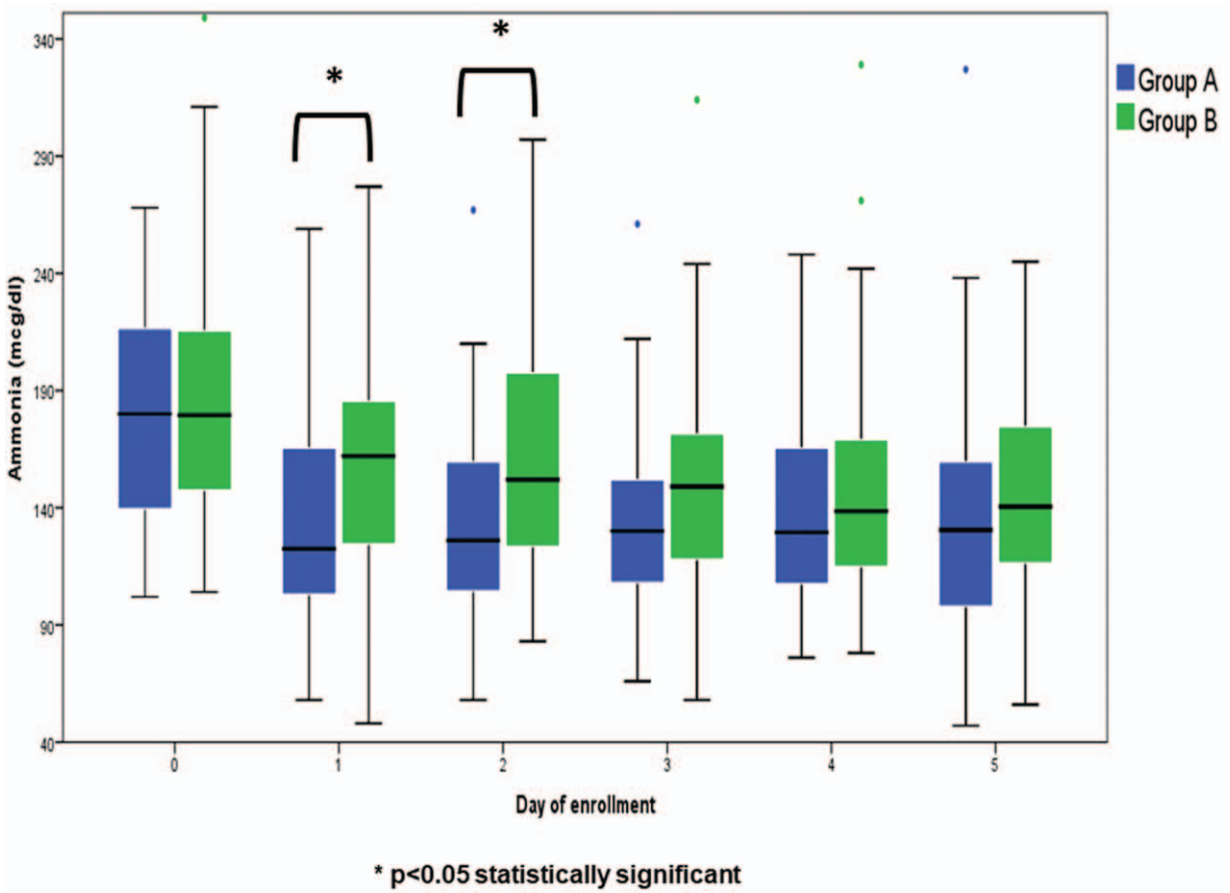

	Group A (n=44)	Group B (n=44)	Mean Difference (95%CI)	p value
Day 0	181.8±47.6	186.3±55.9	-4.6 (-26.6 to 17.4)	0.68
Day 1	136.6±48.5	159.3±50.8	-22.7 (-43.7 to -1.6)	0.003
Day 2	131.4±39.9	165.9±63.2	-34.6 (-57 to -12.2)	0.003
Day 3	135.4±44.1	149.4±44.6	-13.9 (-32.7 to 4.9)	0.144
Day 4	147.9±84	147.8±50.6	0.1 (-29.3 to 29.5)	0.994
Day 5	136.9±51.8	152.7±56.6	-15.7 (-38.7 to 7.2)	0.177

FIGURE 2. Comparison of serum ammonia between groups A and B at all days from days 0 to 5. The ammonia levels in group A was significantly lower as compared to group B at days 1 and 2 of intervention. The ammonia levels were comparable between the 2 groups at baseline and from day 3 onwards after intervention. CI = confidence interval.

lack of difference in resolution of HE in our study could probably be due to the shorter duration of the therapy and follow-up assessment.

Although statistically insignificant, there was higher incidence of adverse effects in sodium benzoate arm as compared to SMT alone. Gastrointestinal side effects have been previously reported with sodium benzoate (17). Nausea (36.4%) and vomiting (31.8%) were more common especially after the first loading dose but did not merit discontinuation of therapy in any. Also, 7 (15.9%) children had increased ascites as compared to 2 (4.5%) children in SMT group. Other side effects seen with sodium benzoate were headache (n = 6), tinnitus (n = 3), and vertigo (n = 3) but were not severe warranting any specific treatment. The rise in serum sodium were similar in both the groups as per the Mann-Whitney *U* analysis ($P = 0.262$). In the study by Sushma et al (15) the incidence of nausea (39.4%) and vomiting (25.8%) were similar as in the present study, although no patient developed increase in ascites. The mean increase in serum sodium (mEq/L) was, however, significantly higher compared to lactulose (mean difference [95% CI]: sodium benzoate 15 [5.7−24.2] vs lactulose 2 [−5.8−9.8]; $P = 0.0001$) (15).

The addition of sodium benzoate did not significantly affect the duration of hospital stay or short-term SNL as was seen in the previous studies (15,18). A recent meta-analysis has shown that nonabsorbable disaccharides such as lactulose have a beneficial

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TABLE 2. Adverse events in the 2 groups during the period of study

	Group A (n = 44)	Group B (n = 44)	OR (95% CI)	*P*
Increased ascites (%)	7 (15.9%)	2 (4.5%)	3.97 (0.77–20.2)	0.157
Nausea (%)	16 (36.4%)	10 (22.7%)	1.94 (0.76–4.94)	0.242
Vomiting (%)	14 (31.8%)	10 (22.7%)	1.58 (0.61–4.09)	0.237
Headache (%)	6 (13.6%)	0	–	0.026
Vertigo (%)	3 (6.8%)	0	–	0.242
Tinnitus (%)	3 (6.8%)	0	–	0.241
Hypernatremia (sodium >145 mEq/L)	0	0	–	–

CI = confidence interval; OR = odds ratio.

effect with respect to serious liver-related adverse events such as liver failure, variceal bleeding, serious infections, spontaneous bacterial peritonitis, and hepatorenal syndrome (relative risk 0.42, 95% CI 0.26–0.69) and causing decrease in hospital admissions and duration of hospital stay unlike seen with the sodium benzoate (23). Hence addition of lactulose in the SMT, which was common to both the arms, can explain no added benefit of sodium benzoate in the present study.

The strength of the present study is that it is the first randomized controlled trial in children on the role of sodium benzoate in HA due to decompensated CLD. Although we did not find significant decrease in the ammonia levels with sodium benzoate at conventional doses, the role of using much higher doses in special situations could be considered with a word of caution considering its adverse effect profile. One major limitation of the study was that the patients were followed up only for 5 days, whereas, changes in clinical parameters such as HE, ascites, and serum sodium could have occurred even after the day 5 of therapy and were not recorded in the data. Another limitation was that we did not have the facility for measuring benzoate levels. To conclude, addition of sodium benzoate did not significantly decrease the ammonia levels except in the first 2 days as compared to the SMT alone. Sodium benzoate caused an increasing trend of adverse events with no effect on duration of hospital stay or short-term SNL.

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