

Clinical trial

Oral rehydration therapy: efficacy of sodium citrate equals to sodium bicarbonate for correction of acidosis in diarrhoea

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SUMMARY Forty patients with moderate degrees of dehydration and acidosis because of acute watery diarrhoea were successfully treated randomly with either WHO recommended oral rehydration solution containing 2.5 g sodium bicarbonate or an oral solution containing 2.94 g sodium citrate in place of sodium bicarbonate per litre of oral rehydration solution. Efficacies were compared by measuring oral fluid intake, stool and vomitus output, change in body weight, hydration status, and rate of correction of acidosis during a period of 48 hours. Seventy five per cent (21 cases) in the citrate group and 83% (19 cases) in the bicarbonate group were successfully rehydrated ($p>0.05$). There were no significant differences in intake, output, gain in body weight, fall in haematocrit and plasma specific gravity, and correction of acidosis between the two groups of patients within 48 hours after initiation of therapy. The solution with sodium citrate base was as effective as WHO-oral rehydration solution for management of diarrhoea. This study shows the efficacy, safety, and acceptability of citrate containing oral rehydration solution for rehydration and correction of acidosis in diarrhoea.

Solutions containing salts of bicarbonate, lactate or acetate are used intravenously for correction of acidosis.^{1,2} Base precursors (lactate, citrate, or acetate) are converted to bicarbonate in the liver within few minutes after intravenous administration.^{3,4} Bicarbonate is absorbed directly from the gut by active transport and corrects acidosis. An important disadvantage of oral rehydration solution containing bicarbonate, however, is that when the constituents are mixed together as solids in a packet in humid atmosphere, bicarbonate reacts with glucose or sucrose to form brownish furfural compounds and thus has shorter shelf life. This may create worry among patients to use it. This is a serious constraint for the propagation of oral rehydration therapy in developing countries. So it is essential to find an alternative without jeopardising its efficacy. Sodium citrate (tribasic) being a stable salt will not give such discolouration, may have

longer shelf life, and may be easier to dispense in tablet form.

In this study, we compared the efficacy acceptability of oral rehydration solution containing sodium citrate with that of sodium bicarbonate in the treatment of dehydration from diarrhoea and concomitant acidosis.

Methods

PATIENTS

The study was carried out at International Centre for Diarrhoeal Disease Research, Bangladesh. The subjects for the study included 18 adults and the 33 children (2-10 years) who were admitted for acute diarrhoea and associated acidosis. The criteria for selection of patients were based on inclusion of patients with moderate degrees of dehydration and acidosis because of acute uncomplicated diarrhoea of less than 48 hours duration who had not received antibiotics before admission. The degree of dehydration and state of acidosis were assessed by WHO guidelines.⁵ To avoid the possible risk of a

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new therapy, young children of less than 2 years old were excluded from the study. Patients were randomly assigned to the two regimens of oral rehydration therapy. Of these patients, 18 children and 10 adults were treated with oral rehydration solution containing sodium citrate and 15 children and eight adults with WHO-oral rehydration solution containing sodium bicarbonate.

No intravenous fluid was given for initial rehydration. All patients were given oral rehydration solution in a volume of 100 ml/kg body weight to be taken within four hours.⁵ Oral rehydration therapy continued to match stool and vomitus outputs until diarrhoea stopped. Mothers or attendants were encouraged to administer oral rehydration solution frequently. Diluted cow's milk (half strength) was given to the patients as diet. Patients were observed by attending physicians and trained nurses regularly in the clinical research ward. Intake of oral rehydration solution, milk, output of stool, urine, and vomitus were measured at four hours interval. The study was conducted up to 48 hours after initiation of therapy. No antibiotics were given.

Blood samples were taken for measurement of haematocrit, plasma specific gravity, and electrolytes on admission before therapy and at four, 24 and 48 hours after initiation of oral rehydration therapy. The CO₂ content was determined on IL 446 CO₂/CL analyser. Na and K determined on IL flame photometer,⁶ plasma specific gravity was measured by Goldberg refractometer. Our biochemistry laboratory uses a quality control system of samples from the World Health Organisation.⁷ A stool sample was obtained for isolation of *Shigella* sp *Salmonella* sp and *Vibrio* sp. Enterotoxigenic *Escherichia coli* were tested for LT⁸ and ST⁹ enterotoxins. Rotavirus detection was not carried out.

Citrate based oral rehydration solution was

prepared with sodium citrate (tribasic) 2.94 g, potassium chloride 1.5 g, sodium chloride 3.9 g and glucose 20 g per litre of water (Na 90, K 20, Cl 80, citrate 30 mmol/l and glucose 110 mmol/l). Patients in the control group received WHO recommended oral rehydration solution, containing same amount of sodium, potassium and chloride and bicarbonate 2.5 g (30 mmol) instead of citrate.

The effect of treatment was assessed by measuring the amount of fluid intake and output (purging and vomiting), gain in body weight, clinical improvement of hydration status and rate of correction of acidosis. Patients whose initial dehydration could not be corrected by oral rehydration solution within four hours and required intravenous fluid therapy were considered as oral therapy failures and excluded from the study. The criteria for failure of treatment by oral rehydration solution based on clinical assessment, supported by intake and output balance, failure to gain body weight and a rise of haematocrit and plasma specific gravity. The failure of oral rehydration solution in correcting acidosis was assessed clinically and confirmed by the laboratory.

The means between the two groups were tested by Student's *t* test.

Results

The two groups of patients were comparable in respect of age, duration of diarrhoea prior to admission, degree of dehydration and acidosis as reflected by haematocrit, plasma sp gravity, and serum carbon dioxide level. Comparison of the means of the above clinico-biochemical characteristics in both children and adults revealed no significant differences ($p > 0.05$), except that children treated with bicarbonate had a higher mean body weight than children treated with citrate oral rehydration solution ($p > 0.02$) (Table 1).

Table 1 Clinical and laboratory characteristics (mean \pm SD) of patients successfully treated with either citrate or bicarbonate containing oral rehydration solution (on admission)

Features	Children (2-10 yr)		Adults (>10 yr)	
	Citrate group (n=13)	Bicarbonate group (n=13)	Citrate group (n=8)	Bicarbonate group (n=6)
Age (yr)	6.1 \pm 2.5	7.1 \pm 2.5	23.3 \pm 11.6	24 \pm 9.8
Duration of diarrhoea (h) (BA) [†]	20.8 \pm 16.6	22.3 \pm 16.6	18.3 \pm 6.8	11.5 \pm 7.6
Weight (kg)	12.4 \pm 2.9	16.5 \pm 5.1*	34.5 \pm 11.9	40.1 \pm 13.3
Haematocrit (%)	43.1 \pm 5.8	45.3 \pm 5.4	47.7 \pm 4.8	50 \pm 2.7
Plasma sp gr	1.030 \pm 0.0032	1.031 \pm 0.0035	1.033 \pm 0.0023	1.032 \pm 0.0024
Serum TCO ₂ (mmol/l)	11.6 \pm 2.2	12.2 \pm 2.9	14.5 \pm 2.3	12.9 \pm 1.5

* $p < 0.02$ by Student's *t* test. [†] BA = before admission.

The effect of treatment with citrate based oral rehydration solution was as successful as that of bicarbonate based oral rehydration solution. There was no difference in rise of serum TCO_2 between the two groups at four, 24 and 48 hours respectively after initiation of therapy ($p>0.05$ for each) (Table 2). Similarly both groups were successfully hydrated with similar rates. Seventy five per cent (21 cases) in the citrate group and 83% (19 cases) in the bicarbonate group were successfully hydrated ($p>0.05$). The success of rehydration in both groups were supported by significant rise in weight, drop in haematocrit and plasma specific gravity. There was no difference between the groups in weight gain, fall in haematocrit and plasma specific gravity at four,

24 and 48 hours after initiation of therapy ($p>0.05$) (Table 3).

There was no significant differences in the amount of intake of oral rehydration solution and output of stool and vomitus between the two groups either in children or in adults (Table 4).

Table 5 shows clinical characteristics of oral therapy failure patients. These patients failed to rehydrate and correct acidosis within four hours after initiation of therapy. Failure of treatment was mostly caused by inability to drink enough of either oral solution for rehydration because of excessive vomiting and purging.

The aetiological agents isolated in these successfully treated patients were *V cholerae* two (10%).

Table 2 Comparison of serum TCO_2 (mean \pm SEM) of patients treated with citrate base oral rehydration solution and bicarbonate base oral rehydration solution ($p>0.05$)

	Children		Adults	
	Citrate group (n=13)*	Bicarbonate group (control) (n=13)*	Citrate group (n=8)*	Bicarbonate group (control) (n=6)*
Serum TCO_2 (mmol/l)				
On admission	11.6 \pm 0.6	12.2 \pm 0.8	14.5 \pm 0.8	12.9 \pm 0.6
at 4 h	16.1 \pm 1.2	16.1 \pm 0.7	19.4 \pm 1.2	17.2 \pm 0.9
at 24 h	18.9 \pm 0.8	21.0 \pm 0.9	21.4 \pm 1.4	21.8 \pm 0.9
at 48 h	21.8 \pm 2.2	23.2 \pm 0.8	27.5 \pm 0.9	25.2 \pm 2.2

* Number of patients studied at 0, 4 and 24 hours time period. Three children and three adults in citrate group and five children and two adults in bicarbonate group were studied at 48 hours time period.

Table 3 Body weight gain and changes in plasma specific gravity and haematocrit (mean \pm SD) of patients treated successfully with either citrate or bicarbonate containing oral rehydration solution at four, 24 and 48 hours

	Children (2-10 yr)		Adults (>10 yr)	
	Citrate group (n=13)*	Bicarbonate group (control) (n=13)*	Citrate group (n=8)*	Bicarbonate group (control) (n=6)*
Body weight gain(%)				
at 4 h	4.2 \pm 3.7	5.1 \pm 3.3	4.3 \pm 3.7	2.6 \pm 2.9
at 24 h	9.6 \pm 5.8	5.6 \pm 3.8	8.2 \pm 3.3	7.6 \pm 4.0
at 48 h	12.5 \pm 2.2	10.1 \pm 4.4	6.6 \pm 3.4	9.8 \pm 2.8
Plasma specific gravity				
at 4 h	1.026 \pm 0.0021	1.027 \pm 0.0032	1.027 \pm 0.0019	1.028 \pm 0.0016
at 24 h	1.024 \pm 0.0021	1.024 \pm 0.0011	1.025 \pm 0.0014	1.025 \pm 0.0023
at 48 h	1.024 \pm 0.0020	1.024 \pm 0.0020	1.025 \pm 0.0009	1.025 \pm 0.0006
Haematocrit (%)				
at 4 h	37.6 \pm 5.5	39.8 \pm 6.7	42.2 \pm 4.9	43.2 \pm 2.5
at 24 h	33.3 \pm 2.5	34.1 \pm 2.7	37.0 \pm 5.6	37.2 \pm 6.0
at 48 h	33.3 \pm 1.5	32.4 \pm 3.6	37.3 \pm 6.0	32.0 \pm 3.0

* Number of patients studied at four and 24 hours time period. Three children and three adults in citrate group, five children and two adults in bicarbonate group were studied at 48 hours time period.

Table 4 Fluid intake and output (mean \pm SD) of patients treated successfully with either citrate or bicarbonate containing oral rehydration solution

	Children (2–10 yr)		Adults (>10 yr)	
	Citrate group (n=13)*	Bicarbonate group (control) (n=13)*	Citrate group (n=8)*	Bicarbonate group (control) (n=6)*
Intake (ml/kg)				
Oral rehydration solution				
0–4 h	82 \pm 33	82 \pm 42	57 \pm 15	48 \pm 15
0–24 h	232 \pm 86	252 \pm 103	178 \pm 60	171 \pm 60
24–48 h	163 \pm 76	242 \pm 123	87 \pm 33	164 \pm 85
Milk				
0–4 h	9 \pm 8	9 \pm 6	3 \pm 3	4 \pm 4
0–24 h	27 \pm 11	19 \pm 9	13 \pm 10	8 \pm 5
24–48 h	12 \pm 13	12 \pm 7	4 \pm 3	6 \pm 1
Output (ml/kg)				
Stool				
0–4 h	18 \pm 21	18 \pm 24	5 \pm 7	6 \pm 9
0–24 h	55 \pm 43	88 \pm 74	24 \pm 21	40 \pm 25
24–48 h	81 \pm 24	97 \pm 67	11 \pm 11	25 \pm 17
Vomit				
0–4 h	19 \pm 32	19 \pm 37	12 \pm 20	7 \pm 11
0–24 h	25 \pm 43	29 \pm 45	14 \pm 23	7 \pm 11
24–48 h	0	0	0	0

* Number of patients studied during 0–4 and 0–24 hours time period. For the time period 24–48 hours, three children and three adults in citrate group and five children and two adults in bicarbonate group were studied.

ETEC 11 (52%) and mixed infection two (10%) in the citrate group, *V. cholerae* nine (47%), *ETEC* six (32%) in the bicarbonate group. Organisms isolated in patients who failed to oral therapy were *V. cholerae* three, *Shigella flexneri* one, in the citrate group and *V. cholerae* four in the bicarbonate group.

Table 5 Comparison of clinical data of oral failure patients on admission and at four hours of therapy (mean \pm SD)

	Citrate group (n=7)	Bicarbonate group (n=4)
Age (yr)	12.1 \pm 9.2 (range 3½–30 yr)	20 \pm 15.7 (range 7–40 yr)
Haematocrit		
On admission	48.4 \pm 6.0	47.2 \pm 2.9
at 4 h	49.0 \pm 4.8	50.7 \pm 1.1
Serum specific gravity		
On admission	1.034 \pm 0.0021	1.037 \pm 0.0022
at 4 h	1.035 \pm 0.0027	1.039 \pm 0.0022
Serum total CO₂		
On admission	12.3 \pm 2.9	14.1 \pm 1.9
at 4 h	13.4 \pm 1.7	11.4 \pm 1.1
Intake (ml/kg)		
Oral rehydration solution	84.3 \pm 55.0	126.4 \pm 75.6
Output (ml/kg)		
Vomit	58.9 \pm 18.7	106.1 \pm 52.5
Stool	35.9 \pm 45.3	13.7 \pm 4.1

Discussion

This study shows that citrate is as effective as bicarbonate in oral rehydration solution for management of dehydration and concomitant acidosis because of acute watery diarrhoea. In this study 75% success rate of oral therapy with citrate base oral rehydration solution is comparable with the success rates obtained from WHO-oral rehydration solution.^{10, 11} The reason for relative high failure rate of therapy in this study is mainly because of the selection of patients with more than moderate degrees of dehydration, high purging, and profuse vomiting in some cholera and cholera like diarrhoea patients which routinely need intravenous therapy. If intravenous fluid had been used for initial rehydration of such patients with purging and persistent vomiting, the oral failure rates could have been reduced considerably.

The children in citrate group had a lower body weight than in bicarbonate group. This could be due to undernourishment of these children as the degree of dehydration as reflected by sp gravity, haematocrit, and body weight gain was similar for both groups.

Both the children and the adults accepted the solution containing citrate as willingly as standard oral rehydration solution containing bicarbonate. Further controlled clinical trials, however, are

needed to be carried out particularly in infants and children under 2 years.

The cost effectiveness of these two oral rehydration solutions has been assessed on the basis of Dhaka market price. The cost of 100 packets of oral rehydration salts containing sodium citrate is US\$8.4 and of bicarbonate is US\$8. The difference in cost may be because sodium bicarbonate is more readily available in the market than sodium citrate. If large amount of citrate based oral rehydration solution is prepared by institutions, the cost definitely will be reduced and even may become cheaper than that of bicarbonate containing oral rehydration solution. In addition, citrate based salt can be easily stored and may be easier to be prepared in tablet form for dispensing. These advantages have particular implications in developing countries where there is great need for general stock piling of oral rehydration solution packets/tablets for use in national oral rehydration programmes.

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