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RESEARCH ARTICLE

Resuscitative Effects of Hyperosmotic Sodium Bicarbonate on Strong Ion Metabolic Acidosis in *Salmonella*-Induced Neonatal Calf Diarrhea in Buffalo Calves

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ABSTRACT

This study evaluated the effectiveness of hyperosmotic sodium bicarbonate (HSB) in ameliorating strong ion difference (SID) and correcting acidemia in experimentally induced buffalo neonatal diarrheic calves. For that purpose, 18 buffalo calves of 14-17 days of age were reared. *Salmonella* broth was introduced orally to the calves for induction of diarrhea. Calves were then randomly assigned to one of the three treatment regimens i.e., group A was treated with normal saline solution (NSS; 0.9% NaCl) @ 60 mL/Kg BW, IV once, group B was administered with hypertonic saline solution (HSS; 7.5% NaCl) @ 5 mL/Kg BW, IV once, while group C administered with HSB (8.4% $NaHCO_3$) @ 5 mL/Kg BW, IV once. All groups were additionally treated with ciprofloxacin @ 7 mg/Kg BW, IV bid and flunixin meglumine @ 2 mg/Kg BW, IV tid for five consecutive days. Efficacy of HSB was assessed through clinical parameters, hematological parameters, blood D- and L-lactates, acid-base variables, and serum electrolytes. All parameters were observed at different time points. Group C showed higher survival than other groups. HSB infusion to neonatal calves of group C significantly ($P<0.05$) reduced blood D-lactate level and ameliorated SID variables than other groups A and B. It is concluded that administration of HSB is highly effective in alkalinizing diarrheic calves with strong ion acidosis thus efficiently reversing metabolic acid-base balance in *Salmonella*-induced neonatal diarrhea in buffalo calves.

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INTRODUCTION

Neonatal calf diarrhea (NCD) has always remained one of the most challenging clinical syndromes and the most common cause of morbidity and mortality in dairy calves (Foster and Smith, 2009; Sen *et al*., 2009). It is one of the leading causes of economic loss to the cattle industry in developing countries (Trefz *et al.,* 2017; Kim *et al*., 2021). Mortality due to NCD in Pakistan varies from 23.7 to 63.0% in buffalo calves (Khan and Zaman, 2007; Zafar *et al.,* 2015; Humayun *et al*., 2021). A major cause of mortality in calves is the development of metabolic acidosis associated with excessive loss of water in feces, electrolytes, especially bicarbonate, and hypovolemia (Berchtold, 1999; Constable *et al*., 2005; Muller *et al*., 2012; Hallowell and Remnant, 2016). Furthermore, D-lactic acidosis has been identified as another important factor in the development of acidemia in diarrheic calves (Ewaschuk *et al*., 2004) because of decreased absorption of the substrate with subsequent formation of D-lactate in the gastrointestinal tract. It is also reported that hyponatremia and D-lactatemia decrease strong ion difference (SID), thereby considered as important contributing factors to cause strong ion acidosis and acidemia directly in diarrheic calves (Constable *et al*., 2005; Kim *et al*., 2021). Although these problems are not distinctive to the calves but the intensity of strong ion acidosis and acidemia is more severe in calves than in other species (Ewaschuk *et al*., 2004).

Intravenous therapy of fluid with electrolytes has long been considered a preferred and practical choice in the resuscitation of acidotic calves associated with diarrhea (Berchtold, 1999; Foster and Smith, 2009). For the last two-decades, the SID approach has been considered while treating acidemic diarrheic calves because it characterizes the alkalinizing ability of intravenous fluids (Constable 2003; Kock and Kaske, 2008). Sodium bicarbonate provides an effective SID approach in correcting strong ion acidosis by increasing the independent variable (Muller *et al*., 2012). Therefore, sodium bicarbonate is regarded as the therapy of choice for treating dehydration, mild to moderate concomitant acidemia, strong ion acidosis in diarrheic neonatal calves (Kasari and Naylor, 1985; Kasari, 1990; Constable, 2003; Constable *et al*., 2021). Effective SID value of 1.4% $NaHCO_3$ is 167 mEq/L whereas 8.4% $NaHCO_3$ has effective SID value of 1,000 mEq/L. Hyperosmotic sodium bicarbonate (HSB; 8.4% $NaHCO_3$) is a small-volume solution that has been identified as fundamental to successful alkalinization and offers fast and effective improvement of severe acid-base abnormalities (Coskun *et al.,* 2010; Constable *et al*., 2021).

Scanty information is available regarding the treatment of NCD with hyperosmotic sodium bicarbonate in buffalo calves in Pakistan. The aim of this study, therefore, was to evaluate the effects of increased load of bicarbonate through small-volume HSB (8.4% $NaHCO_3$) in the resuscitation of buffalo calves with strong ion metabolic acidosis associated with diarrhea.

MATERIALS AND METHODS

Experimental Animals: This study was conducted in accordance with a protocol approved by the Institutional Animal Ethics Committee, PMAS-Arid Agriculture University, Rawalpindi, Pakistan. A total of 18 healthy, dam colostrum-fed, buffalo neonatal calves of 14-17 days old with a mean weight of 30±5 Kg were procured and maintained at University Research Farm, Koont, PMAS-Arid Agriculture University, Rawalpindi. Calves were then acclimatized for five days. Calves were fed on milk replacer through bottles with nipple @ 10 percent of body weight per calf per day.

Instrumentation: The day before induction of diarrhea, calves were sedated with xylazine HCl (Xylaz®, Farvet Laboratories, Holland) for aseptic placement of intravenous catheters. For this purpose, the sites were prepared over the left and right jugular furrow. The areas were then scrubbed with povidone-iodine solution and IV catheters were placed. An 18-gauge catheter was positioned in the right jugular vein for the collection of blood samples. The left jugular vein was catheterized for infusion of fluid and other drugs. After instrumentation, calves were shifted to their stalls. Before induction of *Salmonella* infection, baseline values were recorded.

Induction of diarrhea: After acclimatization of five days, healthy calves were drenched with *Salmonella* broth culture having a *Salmonella* count of 6.5×10^8 CFU mixed with 250 mL of normal saline solution (Fecteau *et al.,* 2003). After 8 to 10 h, diarrhea was induced successfully in calves of all groups. Treatment was then instituted when calves achieved the inclusion criteria i.e., 10% dehydration, skin tenting time >5 but <10 sec and markedly recession (6-8 mm) of eyeball in orbit (Muller *et al*., 2012).

Study design: The neonatal buffalo calves were then randomly assigned to different treatment protocols as follow:

- **Group A** was treated with normal saline solution (NSS; 0.9% NaCl) @ 60 mL/Kg BW, IV once.
- **Group B** was administered with hypertonic saline solution (HSS; 7.5% NaCl) @ 5 mL/Kg BW, IV followed by NSS @ 10 mL/Kg BW, IV once.
- **Group C** was treated with HSB (8.4% $NaHCO_3^-$, Natriumhydrogencarbonat, Sigma-Aldrich, Steinheim, Germany) @ 5 mL/Kg BW, IV followed by NSS @ 10 mL/Kg BW, IV once.

In addition, calves of all groups were also administered with ciprofloxacin (Novidat®, Sami Pharmaceuticals Pvt. Ltd. Karachi, Pakistan) @ 7 mg/Kg BW, IV bid and flunixin meglumine (Tricure®, ICI Pakistan Limited) @ 2 mg/Kg BW, IV tid for five consecutive days.

Measurements and analyses of samples: Clinical parameters (survival rate, body temperature, respiratory rate and heart rate), hematological parameters (hematocrit and hemoglobin concentration), blood lactates (L-lactate and D-lactate), acid-base variables [bicarbonates, blood pH, anion gap (AG) and strong ion difference (SID_3)], serum electrolytes (sodium ions conc., potassium ions conc., chloride ions conc.) were measured to estimate the resuscitative effects of HSB in comparison to NSS and HSS in *Salmonella*-induced neonatal calf diarrhea. For hematocrit (Hct) and hemoglobin concentration (Hb conc.) analyses, 2 mL of blood was collected in evacuated tubes that contained EDTA and were determined by a hematology analyzer (Biochemistry Analyzer, USA). Blood lactates were determined by using spectro-photometer (Lorenz, 2009). Concentration of serum electrolytes, bicarbonate and blood pH were measured through Blood Gas Analyzer (Epoc®, Epocal Inc., Canada). An estimate of the unmeasured anion concentration was obtained by calculating the anion gap (AG) in mEq/L, whereby:

$$AG = (cNa^+ + cK^+) - (cCl^- + cHCO_3^-)$$

The strong ion difference in mEq/L calculated from serum concentrations of sodium, potassium and chloride (SID_3) was obtained as follows (Hallowell and Remnant, 2016):

$$SID_3 = ([cNa^+] + [cK^+]) - [cCl^-]$$

Measuring interval: All aforementioned parameters were noted at baseline (before induction of diarrhea), during the course of diarrhea, t-3 h, t-9 h, t-18 h, t-36 h, t-72, t-120 h and t-168 h after institution of allocated treatment.

Statistical analyses: The data obtained were analyzed through Completely Randomized Design (CRD). The significant difference within and between groups was analyzed through Tukey's test.

RESULTS

1. Clinical parameters: No mortality was observed in any group after induction of diarrhea with Salmonella broth to the buffalo calves. After administration of allocated treatment, calves of groups A and B showed mortality, while group C showed a better survival rate with no mortality (Table 1). Induction of diarrhea with Salmonella induced a significant ($P<0.05$) increase in body temperature and heart rate, while a decrease in respiration rate of buffalo calves in all groups. After administration of allocated treatment regimens, a decreasing trend was observed in the body temperature and heart rate of calves of all groups. However, group C showed a significant (P<0.05) difference over group A at t-3 h in both body temperature and heart rate (Table 1). Whereas an increasing trend in respiration rate was observed in all groups after treatment, but group C showed a rapid and significant (P<0.05) difference over both of its counterparts throughout the study period except at t-120 h and recovered the basal values at t-36 h, whereas groups A and B were failed to recover baseline values within the study period (Table 1).

2. Hematological parameters: Values of hematocrit (Hct) and hemoglobin concentration (Hb conc.) increased in all groups during diarrhea. Treatment institution assisted in decreasing their values in all groups which was significant (P<0.05) in group C at t-3 h. The decreasing trend continued in all groups till they achieved baseline values (Table 1).

3. Blood lactates: A non-significant difference was observed in the values of blood lactates (L-lactate and D-lactate) prior to *Salmonella* infection. Induction of neonatal diarrhea increased mean values of both lactates from baseline. After the institution of allocated treatment, the trend of mean values of both blood lactates started to decline toward recovery, however, group C showed a sharp recovery trend than its counterparts. All groups continued their recovery trend and achieved baseline within the study period (Table 1).

4. Acid-base variables: Values of bicarbonate and blood pH decreased in all groups during diarrhea. After administration of allocated treatments, trend of both parameters was toward recovery. However, a better recovery trend was observed in group C and it attained the baseline values of bicarbonate (Fig. 1A) and blood pH successfully (Fig.1B), while other groups showed near to basal values at the end of the study. The anion gap (AG) in neonatal calves increased non-significantly in all groups during diarrhea. After the institution of allocated treatments, calves of group A showed a normal trend toward baseline values with some fluctuation at different time points. At the same time, groups B and C showed a significant (P<0.05) increase up to t-36 h. These values of the anion gap decreased afterwards and attained the basal values within the study period. Group A showed a significant (P<0.05) trend over both of its counterparts (Fig. 1C). Whereas the values of strong ion difference (SID_3) in neonatal buffalo calves of all three groups decreased non-significant. After the institution of allocated treatment, calves of group C showed a gradual increase in the values of SID_3 up to t-36 h. A constant and significant (P<0.05) decrease was observed afterwards which continued till the end of study and successfully attained the baseline values (Fig. 1D).

5. Serum electrolytes: At baseline, values of serum sodium (Na^+), potassium (K^+) and chloride (Cl^-) concentrations were non-significantly different in all three groups which dropped significantly in diarrheic condition. After administration of treatment protocol, a variable statistical difference was observed within groups A, B and C. Group A showed a non-significant difference at each time point throughout the study period in Na^+ (Fig. 2A), K^+ (Fig. 2B) and Cl^- (Fig. 2C) concentrations. Group B showed variable values during study. Group C revealed a significant (P<0.05) rise in values of serum Na^+, K^+ and Cl^- values at different time points and achieved baseline values earlier than its counterparts (Fig. 2A, 2B and 2C, respectively).

Table 1: Results of clinical, hematological and blood lactates in *Salmonella*-induced neonatal calf diarrhea in response to different treatment regimens

Variables		Time after treatment								
	Groups	Baseline	Diarrhea	t-3 h	t-9 h	t-18 h	t-36 h	t-72 h	t-120 h	t-168 h
Survival Index (%)	Group A	100	100	100	83.33	83.33	66.67	66.67	66.67	66.67
	Group B	100	100	100	100	100	83.33	83.33	83.33	83.33
	Group C	100	100	100	100	100	100	100	100	100
Body Temperature (ºC)	Group A	38.59±0.15def	40.11±0.26a	39.33±0.11bc	38.98±0.15cde	38.52±0.15ef	38.40±0.12f	38.40±0.06f	38.46±0.08ef	38.61±0.12def
	Group B	38.66±0.09def	39.37±0.17bc	39.11±0.07cd	38.37±0.12f	38.73±0.07def	38.31±0.06f	38.18±0.04f	38.28±0.08f	38.44±0.06ef
	Group C	38.59±0.10def	39.74±0.14ab	38.66±0.06def	38.39±0.05f	38.50±0.08ef	38.31±0.04f	38.37±0.06f	38.31±0.07f	38.42±0.05ef
Respiration Rate (breaths/min)	Group A	30.50±0.56a-d	21.00±0.73j	21.67±0.61ij	22.33±0.67hij	25.50±0.99fgh	25.67±0.84fgh	27.00±0.89d-g	29.33±0.61b-e	29.33±0.61b-e
	Group B	31.00±0.73abc	21.00±0.73j	22.83±0.75hij	25.00±0.68ghi	27.00±0.89d-g	26.83±0.87efg	27.50±0.89c-g	29.33±0.76b-e	30.50±0.56a-d
	Group C	32.17±0.48ab	20.33±0.61j	27.17±0.40d-g	28.67±0.49b-f	30.17±0.60a-e	31.33±0.49ab	31.17±0.31ab	31.67±0.56ab	33.17±0.40a
Heart Rate (beats/min)	Group A	86.67±1.23j	106.67±0.99ab	99.67±0.95cde	98.33±0.61c-f	93.67±1.58e-i	93.33±1.52f-i	92.33±0.61f-j	87.67±0.95ij	86.67±0.99j
	Group B	92.33±1.50f-j	108.33±1.20ab	102.67±1.23bc	100.00±0.73cd	99.67±0.80cde	97.67±0.95c-f	94.33±1.20d-h	90.67±0.99g-j	90.33±1.58hij
	Group C	90.33±1.20hij	111.33±1.91a	98.00±1.93c-f	95.67±1.41d-h	96.67±0.67c-g	95.00±0.86d-h	93.67±1.09e-i	91.33±0.84g-j	90.00±1.15hij
Hematocrit (%)	Group A	37.50±0.76d-i	47.50±1.34ab	45.17±1.42abc	41.83±1.14cd	39.17±0.70d-g	36.33±0.67f-i	36.17±1.60ghi	31.17±0.79j	32.67±1.15ij
	Group B	35.17±0.91g-j	49.17±0.60ab	44.50±1.18bc	41.33±0.80cde	38.17±0.60d-h	36.50±0.85e-i	33.50±0.99hij	32.83±0.70ij	33.67±0.95hij
	Group C	35.83±0.79g-j	49.83±0.60a	41.17±0.87c-f	37.50±0.72d-i	37.17±0.87d-i	34.83±0.60g-j	33.33±0.92hij	34.67±1.02g-j	36.50±0.56e-i
Hemoglobin Concentration (g/dL)	Group A	9.25±0.38cd	13.67±0.67ab	11.25±0.54c	11.33±0.73bc	10.67±0.48cd	9.92±0.35cd	9.62±0.24cd	8.98±0.26cd	8.83±0.25d
	Group B	9.75±0.38cd	14.17±0.79a	10.53±0.74cd	10.17±0.38cd	9.33±0.57cd	8.83±0.44d	9.03±0.38cd	9.07±0.20cd	9.50±0.34cd
	Group C	9.48±0.29cd	13.67±0.67ab	9.62±0.53cd	9.57±0.38cd	9.12±0.36cd	9.07±0.24cd	9.10±0.19cd	9.15±0.28cd	9.75±0.34cd
L-Lactate (mmol/L)	Group A	2.33±0.15ij	3.49±0.11cde	3.88±0.16bc	3.57±0.14b-e	3.49±0.15cde	3.12±0.10d-h	2.78±0.09f-i	3.23±0.08c-g	2.58±0.10g-j
	Group B	2.55±0.21g-j	3.54±0.13b-e	4.63±0.11a	3.42±0.12c-f	3.07±0.15d-h	3.23±0.11c-g	3.07±0.13d-h	2.92±0.16e-i	2.78±0.15f-i
	Group C	1.99±0.14j	3.46±0.09c-f	4.85±0.15a	4.22±0.14ab	3.63±0.16bcd	3.22±0.08c-g	2.67±0.15g-j	3.46±0.09c-f	2.52±0.10hij
D-Lactate (mmol/L)	Group A	2.02±0.11op	5.18±0.08a	4.98±0.11ab	4.62±0.12bc	4.02±0.08def	3.58±0.07fgh	3.02±0.07jkl	3.10±0.07i-l	2.48±0.10mno
	Group B	1.72±0.09p	5.25±0.09a	4.87±0.09ab	4.37±0.10cd	3.97±0.08def	3.55±0.06f-i	3.17±0.03h-l	3.22±0.10h-k	2.32±0.07no
	Group C	2.13±0.10op	5.28±0.10a	4.98±0.09ab	4.25±0.13cde	3.88±0.10efg	3.48±0.07g-j	2.95±0.06klm	2.73±0.08lmn	2.30±0.13no

*Indicates statistically significant (P<0.05) difference of that group over the others which does not contain it. Means ± SE sharing similar letters within each group are non-significant.

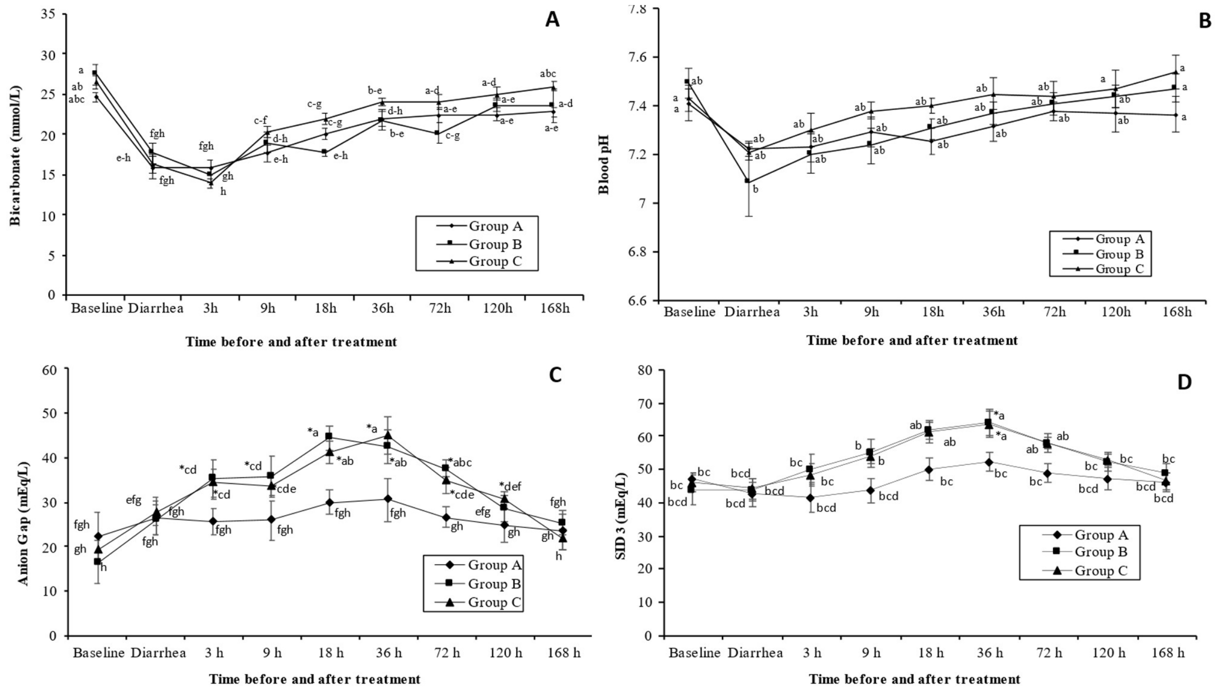

Fig. 1: (A) Biocarbonate (mmol/L), (B) Blood pH, (C) Anion Gap (mEq/L) and (D) Strong ion difference (mEq/L) in Salmonella-induced neomatal calf diarrhea in response to different treatment regimens. *Indicates statistically significant (P<0.05) difference among groups A, B, and C at each time point. Means ± SE sharing similar letters within group are non-significant.

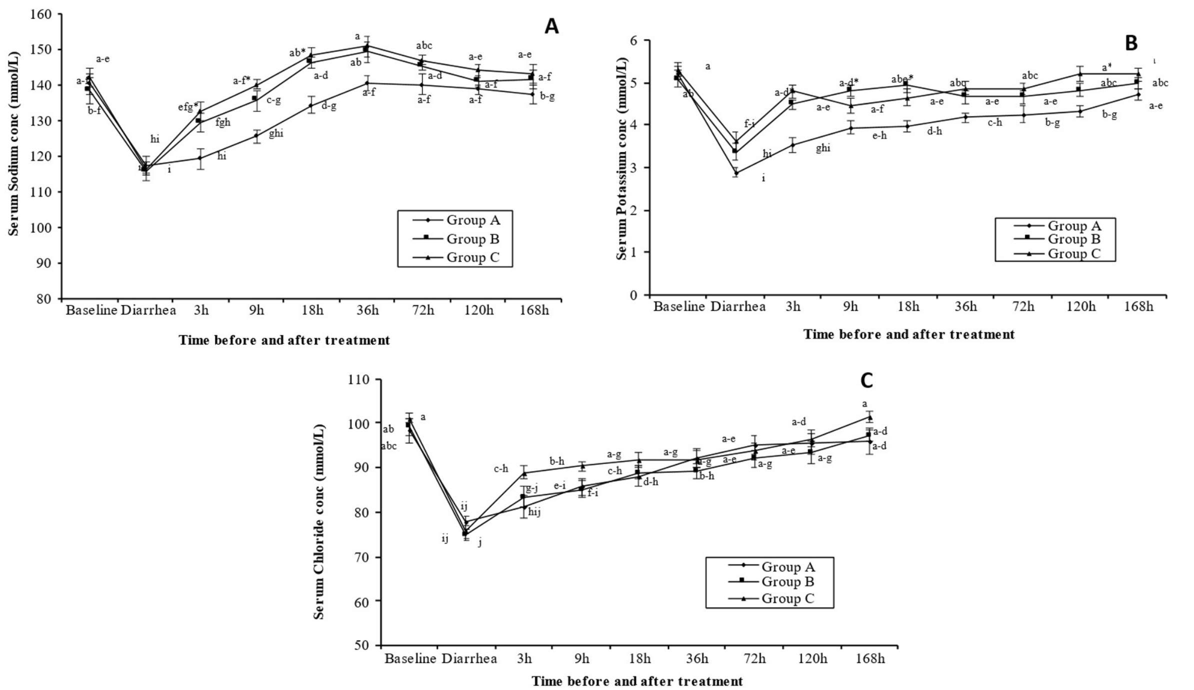

Fig. 2: (A) Serum sodium concentration (mmol/L), (B) Serum potassium concentration (mmol/L) and (C) Serum chloride concentration (mmol/L) in Salmonella-induced neomatal calf diarrhea in response to different treatment regimens. *Indicates statistically significant (P<0.05) different among groups A, B, and C at each time point. Means ± SE sharing similar letters within group are non-significant.

DISCUSSION

The current study was directed to evaluate the resuscitative effects of HSB (8.4% $NaHCO_3$) in the amelioration of strong ion acidosis in diarrheic calves and to compare it with NSS (0.9% NaCl) and HSS (7.5% NaCl). The diarrhea was induced in all calves through oral administration of *Salmonella* broth. A severe dehydration around 10%, skin tenting of >5 sec and <10 sec and markedly recession (6-8 mm) of eyeball in orbit were the cut-off point for starting a treatment protocol. Due to diarrhea in calves, a decline in extracellular fluid volume occurred, resulting in depletion of plasma volume (Zafar *et al*., 2015). The purpose of the treatment with fluid and electrolytes to dehydrated diarrheic calves is to reinstate plasma volume quickly. In this study, increased heart rate was observed in diarrheic calves. An increase in heart rate has been correlated with earlier studies that reduction in plasma volume encourages sympathetic nervous system through peripheral vasoconstriction and in response to this heart rate increases. Likewise, it activates the aldosterone system to sustain balance of heart and organ damage (Bleul *et al*., 2007; Zafar *et al*., 2015; Trefz *et al*., 2017). In present study, heart rate became normal rapidly after the institution of HSB to calves of group C due to activation of the circulatory reflex mechanism, increased serum osmolarity and an abrupt rise in plasma volume (Bleul *et al*., 2007). Similarly, the survival index was better in group C, in which no mortality was observed.

The outcomes of the current study showed increased Hct and Hb conc. in severely dehydrated buffalo calves suffering from the severe diarrheic condition. Comparable result discussed in earlier studies show that rise in Hb conc. and Hct is the cause of decreased plasma volume (Zafar *et al*., 2015; Humayun *et al*., 2021; Kim *et al*., 2021). After treatment of calves of group C, Hct and Hb conc. values decreased quickly towards normal, which directs that fluid reinstate dynamic response for plasma volume (Berchtold *et al*., 2005). These results can be compared with the previous studies that HSB provides the rapid method for resuscitation in animals suffering from hypovolemia and because it gives momentary hyperosmolality brought by HSB administration that speedily expands the plasma volume and quickly resuscitates the calves (Berchtold *et al.,* 2005; Zafar *et al*., 2015; Humayun *et al*., 2021).

L-lactate is generally formed during anaerobic respiration by mammalian cells. Its levels in the blood detects the oxygen deprivation in the tissues. In the current study, the serum L-lactate concentrations increased during the course of diarrhea. Bolus IV infusions with hypertonic sodium bicarbonate resulted in a statistically significant decrease in L-lactate concentration, correlated with the findings of Trefz *et al*. (2017). D-lactic acid is an important and major contributor to acidemia in neonatal diarrheic calves. D-lactate is produced in the intestine of the diarrheic calves (Ewaschuk *et al*., 2004; Gentile *et al*., 2004; Constable *et al.,* 2005). In the current study, hyper D-lactatemia was observed in diarrheic calves, representing that D-lactic acidosis contributes to calves with high anion gap acidosis. In animals, it cannot be efficiently removed from the blood through metabolic pathways. It is metabolized to pyruvate by D-α-hydroxy acid dehydrogenase and excreted by the kidneys (Omole *et al*., 2001). Both D- and L-lactates mutually interfere with their renal tubular reabsorption, therefore, low kidney perfusion would likely increase reabsorption, thus resulting in increased concentration of serum D-lactate. In this study, IV administration of HSB showed rapid correction of hyper D-lactatemia in diarrheic buffalo calves. AG and SID increased in neonatal buffalo calves after induction of *Salmonella*-induced diarrhea; this may be because D-lactate and L-lactate contribute to the elevation of the AG in diarrheic calves (Omole *et al.,* 2001; Muller *et al*., 2012). Administration of HSB (8.4% $NaHCO_3$) solutions helps quick removal of D-lactate thus helped in resuscitating neonatal diarrheic calves (Ewaschuk *et al*., 2004; Lorenz, 2009; Naylor, 2009; Constable *et al*., 2005). The SID approach to acid-base balance suggests that high effective SID of hyperosmotic sodium bicarbonate (8.4%) solution corrects the strong ion acidosis and metabolic acidemia by increasing the independent variable SID which is witnessed by values of blood pH in this study.

In the present study, hyponatremia and hypochloremia were detected in neonatal diarrheic calves as reported in previous studies (Berchtold *et al.,* 2005; Naylor, 2009; Constable *et al*., 2005; Zafar *et al*., 2015; Kim *et al*., 2021). Intravenous bolus HSB administration caused a rapid increase in serum sodium, potassium and chloride concentration (Berchtold *et al.,* 2005; Coskun *et al*., 2010; Trefz *et al*., 2017). The peak value of serum sodium that was observed in the current study after IV bolus administration of HSB was 150.67±2.76 mmol/L in neonatal buffalo calves. However, use of HSB is conflicting in chronic hyponatremia patients as it develops the neurological problems (Bleul *et al*., 2007; Kock and Kaske, 2008). No change in the attitude and overall behaviour of the neonatal buffalo calves was detected after IV administration of HSB in the current study.

Conclusions: Based on the finding of this study, it is concluded that bolus IV administration of small-volume HSB (8.4% $NaHCO_3$) is highly effective in alkalinizing diarrheic calves with strong ion acidosis thus efficiently reversing metabolic acid-base balance in *Salmonella*-induced neonatal diarrhea in buffalo calves.

Authors contribution: AH conducted the trial and recorded the data. MAZ presented an idea, planned and monitored the whole study. AY and MuH helped to manage the trial and facilitated laboratory work.

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