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Hypoglycemia and failure of respiratory compensation are risk factors for mortality in diarrheic calves in Hokkaido, northern Japan

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ABSTRACT. The aim of present study was to identify risk factors among laboratory findings for mortality in calves with diarrhea. A retrospective analysis was conducted utilizing medical records of 221 diarrheic calves (10.4 ± 3.7 days old) with no concurrent severe disorders that were treated with intravenous fluid therapy from the initial examination. Thirty-eight of the diarrheic calves (17.2%) died within 35 days from the initial examination. Multivariate logistic regression analysis indicated that hypoglycemia (OR 3.09; 95% CI 1.22–7.87; P=0.02) and failure of respiratory compensation (OR 2.63; 95% CI 1.05–6.62; P=0.04) were the major risk factors associated with a negative outcome in diarrheic calves. According to the Kaplan-Meyer analysis, diarrheic calves with hypoglycemia and/or failure of respiratory compensation had a significantly shorter survival than calves without these factors.

KEY WORDS: calf, diarrhea, mortality, risk factor

Diarrhea in neonatal calves remains the leading cause of mortality. Diarrhea leads to overall loss of not only electrolytes and water, but also decreases absorption of carbohydrates, lipids, and amino acids in calves [6]. As a result, calves experience acute symptoms of dehydration, electrolyte imbalance, metabolic acidosis, and negative energy balance. Intravenous (IV) fluid therapy is important for decreasing the mortality associated with diarrhea in calves. Based on current knowledge, IV fluid therapy must satisfy the following three requirements: (1) supply sufficient sodium to normalize the extracellular fluid volume; (2) provide an alkalinizing agent to correct the metabolic acidosis; and (3) provide energy because most calves with diarrhea are in a state of negative energy balance [6].

Previous studies demonstrated that increased serum urea, hematocrit, chloride concentrations [13], acidemia, hypoglycemia, and hypernatremia [30] were risk factors for mortality in diarrheic calves. Trefz *et al*. [29] indicated that severe hypoglycemia was present in only 6.3% of cases, but resulted in a mortality rate of 79.4% in 10,060 neonatal hospitalized calves. The high mortality rate in calves with hypoglycemia can be explained by serious health conditions associated with this metabolic imbalance, including malnutrition [29]. Similarly, diarrhea remains a major cause of death in children under the age of five years worldwide [21]. Talbert *et al*. [25] reported that hyponatremia, hypoxia, hypokalemia, and malnutrition were risk factors for death, and children with malnutrition due to diarrhea in particular had a higher risk of death. [23, 25, 28]. Protein energy malnutrition was found to be a serious issue associated with death in diarrheic children [27]. Bacterial infection is more common with severe malnutrition, and is thought to occur, in part, because of immunosuppressive effects and the loss of the protective mucosal barrier in the gastrointestinal tract [8]. In an effort to address the high child mortality, the World Health Organization (WHO) provides a guideline to improve management for children with malnutrition [32]. Therefore, many pediatric hospitals conforming to the WHO guidelines have succeeded in reducing the mortality of children with malnutrition due to diarrhea [3, 12].

Although our understanding of the pathophysiology [14] and fluid therapy, especially replacement of fluid loss and correction of acid-base balance [6, 24], for diarrheic calves has progressed, mortality rates have remained unchanged for several decades [18, 19, 30]. This suggests the importance of the next step for treatment of diarrheic calves. However, there is a lack of systematic reporting

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of laboratory data to identify risk factors that allow for comparative studies of the burden, spectrum, and outcome of diarrheic calves. Identification of risk factors will help form prospective treatments or change management to improve outcome. Indeed, epidemiologic research may be useful to find new methods, but there is very little epidemiologic research to advance treatments for diarrheic calves. The aim of present study was to identify risk factors among laboratory findings in calves with diarrhea. These data may be useful information for treatment of calves with diarrhea.

MATERIALS AND METHODS

All procedures were in accordance with the National Research Council Guidelines for the Care and Use of Laboratory Animals (National Academy Press, 1996). A retrospective analysis was conducted utilizing medical records of 221 diarrheic calves (10.4 ± 3.7 days old) with no concurrent severe disorder that were treated with intravenous fluid therapy from the initial examination at the Minami Hokkaido Agricultural Mutual Relief Association, Hokkaido (140°E, 42°N) between January 2015 and September 2017. Of these calves, 96 (43.4%) were Holstein, 65 (29.4%) were the first filial generation of a Japanese Black, and 60 (27.1%) were Japanese Black. Most of these calves had been treated such as oral electrolyte solutions, antimicrobial and probiotics in farms before medical treatment by veterinarian. Clinical signs of eyeball recession into the orbit and impaired central nervous system function, including absent suckling reflex, ataxia, and coma, were the main observations for these calves. All calves received an intravenous (IV) fluid therapy consisting of saline, acetate Ringer's, 7.0% sodium bicarbonate, and glucose from the initial examination. The IV fluid therapy was continued until recovery from clinical signs of metabolic acidosis and dehydration. In addition, antimicrobial or anti-inflammatory therapy was carried out for 195 (88.2%) and 83 (37.6%) calves, respectively. The IV fluid therapy or supportive therapy was continued until calves were discharged in a healthy state.

Normally, all calves were offered two feedings of milk at the rate of 5% of body weight per feeding in the morning (a.m. 5:00−a.m. 8:00) and afternoon (p.m. 5:00−p.m. 8:00), but 205 of the diarrheic calves (92.8%) in this survey fall into anorexia. The amount of last milk which calves drunk is unknown, but blood collections was done at least two hours after the providing milk for calves. Venous blood samples were anaerobically collected in a heparinized 1 m*l* syringe from the left jugular vein, and the tips of the syringes capped after collection before the IV fluid therapy. All calves underwent a blood analysis including blood pH, carbon dioxide partial pressure (PCO_2), bicarbonate (HCO_3^-), base excess (BE), anion gap (AG), sodium (Na), potassium (K), chloride (Cl), urea (BUN), glucose (Glu), hematocrit (Ht), and hemoglobin (Hb) concentrations using an automatic gas analyzer (i-STAT 1, Abbott Lab, Princeton, IL, U.S.A.) and i-STAT cartridge (i-STAT EC8+ Cartridge, Abbott Lab) at the initial examination.

Statistical analysis: Statistical analysis was conducted using Excel Toukei 2010 (SSRI, Osaka, Japan). Normally distributed data are reported as the mean ± standard deviation (SD), and non-normally distributed data (total treatment periods, plasma glucose concentration and blood pH) are expressed as the median and ranges. Calves were divided into two groups based on the survival period (until 60 days) from the initial examination (Survival group or Non-survival group). The student's t-test or Mann-Whitney U-test after the F-test was used for comparisons of blood data between groups. Multivariate association between categorized variables and outcome of therapy was evaluated by logistic regression analysis with calculation of odds ratios (OR) and associated 95% confidence intervals (95% CI). In addition, the overall survival time (OST) was calculated as the time between the initiation of treatment and death resulting from diarrhea. The OST curves were estimated by Kaplan-Meyer statistics for the different groups of diarrheic calves with or without risk factors for mortality. The OST among different groups of diarrheic calves was compared using the Bonferroni test after the log-rank test. ROC curves were also used to characterize the sensitivity and specificity of each parameter with respect to changes associated with a negative outcome. The optimal cut-off point for each test was calculated by the Youden index [2]. The Youden index (J) is defined as the maximum vertical distance between the ROC curve and diagonal or chance line, and is calculated as J=maximum [sensitivity+specificity−1]. The cut-off point on the ROC curve corresponding to J was regarded as the optimal cut-off point [2]. The significance level was set at $P<0.05$.

RESULTS

Thirty-eight of the diarrheic calves (17.2%) died until 60 days from the initial examination. Therefore, 183 and 38 diarrheic calves were in the survival group and non-survival group, respectively. The survival rate of the 221 diarrheic calves in this survey was 82.8% (183/221). The total treatment periods were significantly longer in the non-survival group (7.0 days, min to max, 2–34 days) than those in the survival group (5.0 days, 1–22 days, $P<0.05$). During the IV fluid therapy for the diarrheic calves from the initial examination, the total fluid volume was significantly higher in the non-survival group than in the survival group (5,186.8 ± 1,581.9 vs 4,344.6 ± 1,416.1 m*l*, $P=0.006$). However, there were no significant differences in the volume of 7.0% sodium bicarbonate solution (437.6 ± 187.7 vs 400.9 ± 197.0 m*l*, $P>0.05$), glucose (82.1 ± 62.5 vs 81.8 ± 61.8 g, $P>0.05$), and glucose per total fluid volume (1.6 ± 1.2 vs 2.0 ± 1.5%, $P>0.05$) between groups. Total IV fluid therapy periods were significantly longer ($P<0.001$) in the non-survival group (5.0 ± 1.0 days) than in the survival group (2.4 ± 2.0 days).

The results of the blood analysis are summarized in Table 1. The plasma Na ($P=0.04$) and Cl ($P=0.04$) concentrations, and PCO_2 ($P=0.001$) were significantly higher in the non-survival group. On the other hand, blood pH ($P=0.04$) and plasma glucose concentrations ($P=0.02$) were significantly lower in the non-survival group. There were no other significant differences in the blood analysis data.

The following blood analysis parameters were categorized at the initial examination for multivariate logistic regression analysis based on the reference values (ref) in Table 2. Multivariate logistic regression analysis indicated that hypoglycemia (OR 3.09; 95%

Table 1. Laboratory findings for survival and non-survival groups

		Survival (n=183)	Non-survival (n=38)	*P*-value
Na	(mmol/*l*)	132.1 ± 8.7	135.5 ± 10.4	0.04
K	(mmol/*l*)	5.6 ± 1.3	6.1 ± 1.6	NS
Cl	(mmol/*l*)	106.0 ± 10.0	109.8 ± 11.8	0.04
BUN	(mg/d*l*)	48.9 ± 37.5	60.4 ± 38.4	NS
Glu	(mg/d*l*)	82.5 (34–192)	70.5 (19–263)	0.02
Ht	(%)	34.2 ± 8.7	37.1 ± 9.7	NS
Hb	(g/d*l*)	11.6 ± 2.9	12.6 ± 3.3	NS
pH		7.11 (6.69–7.43)	7.05 (6.66–7.45)	0.04
PCO_2	(mmHg)	42.6 ± 11.8	50.0 ± 12.6	0.001
HCO_3^-	(mmol/*l*)	14.6 ± 7.0	14.8 ± 6.4	NS
BE	(mmol/*l*)	–14.9 ± 8.8	–15.7 ± 8.9	NS
AG	(mmol/*l*)	17.3 ± 4.5	16.8 ± 4.7	NS

Table 2. Risk factors among laboratory findings for mortality in diarrheic calves

Variable (n=221)	Variable category	Odds ratio	95% confidence interval	*P*-value	Reference
Sodium concentration (mmol/*l*)	138.8–144.0	1.00	-	-	[15]
	<138.8	0.44	0.16, 1.25	NS	
	>144.0	0.43	0.09, 1.93	NS	
Chloride concentration (mmol/*l*)	100.3–107.0	1.00	-	-	[15]
	<100.3	0.47	0.14, 1.55	NS	
	>107.0	0.95	0.34, 2.64	NS	
Glucose concentration (mg/d*l*)	68.0–90.0	1.00	-	-	[22]
	<68.0	3.09	1.22, 7.87	0.02	
	>90.0	1.12	0.41, 3.07	NS	
Blood pH	≥7.20	1.00	-	-	[5]
	<7.20	1.64	0.58, 4.68	NS	
Carbon dioxide partial pressure (mmHg)	39.8–50.3	1.00	-	-	[7]
	<39.8	0.49	0.18, 1.32	NS	
	>50.3	2.63	1.05, 6.62	0.04	

CI 1.22–7.87; P=0.02) and failure of respiratory compensation (OR 2.63; 95% CI 1.05–6.62; P=0.04) were the major risk factors associated with a negative outcome in diarrheic calves. However, no differences were found for blood pH or plasma Na and Cl concentrations.

Figure 1 shows the OST from the initiation of treatment for diarrheic calves with or without risk factors associated with a negative outcome. At the end point of the survey 60 days from the initial examination, 8 of 111 (7.2%) diarrheic calves without risk factors had died. On the other hand, 13 of 51 (25.5%) and 12 of 48 (25.0%) diarrheic calves with risk factors for hypoglycemia (<68.0 mg/d*l*, [15]) and failure of respiratory compensation (>50.3 mmHg, [7]), respectively, had died. Similarly, at the end point of the survey, 5 of 11 (45.5%) diarrheic calves demonstrated that hypoglycemia and failure of respiratory compensation were the major risk factors for mortality. Therefore, based on the survival estimated by Kaplan-Meyer analysis, diarrheic calves with risk factors had a significantly shorter (P<0.05) survival than calves without.

The areas under the ROC curve for PCO_2 and plasma glucose concentration were 0.678 (P<0.01) and 0.384 (P<0.05), respectively. The proposed diagnostic cut-off point for PCO_2 and plasma glucose concentration for non-survival progression of diarrheic calves were set at >46.9 mmHg and <71.5 mg/d*l*, respectively (Fig. 2). The sensitivity and specificity of the proposed diagnostic cut-offs for PCO_2 were 68.4 and 68.9%, respectively. The sensitivity and specificity of the proposed diagnostic cut-offs for plasma glucose concentrations were 53.3 and 70.5%, respectively. As a result of the multivariate logistic regression analysis using the cut-off values for a negative outcome in diarrheic calves, hypoglycemia (OR 4.11; 95% CI 1.87–9.04; P<0.001) and failure of respiratory compensation (OR 6.07; 95% CI 2.71–13.6; P<0.001) were finally extracted.

DISCUSSION

In this survey, we demonstrated that hypoglycemia and failure of respiratory compensation are the major risk factors associated with a negative outcome in diarrheic calves by multivariate logistic regression analysis. According to Kaplan-Meyer statistics, diarrheic calves with hypoglycemia and/or failure of respiratory compensation had a significantly shorter survival than calves without.

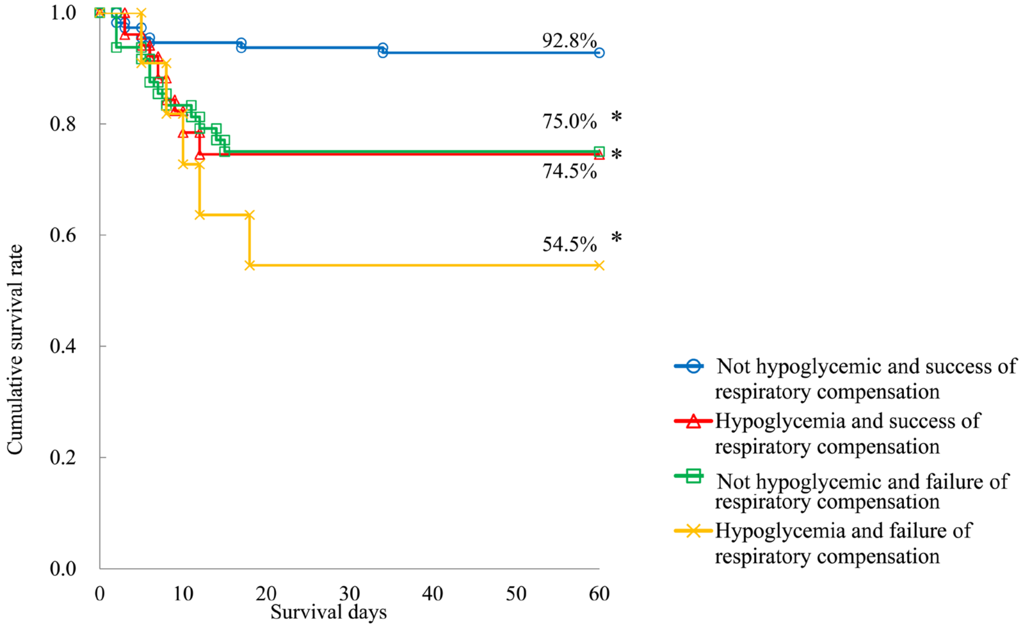

Fig. 1. Graphs depicting the overall survival time (OST) from the initiation of treatment in diarrheic calves with or without risk factors associated with a negative outcome by Kaplan-Meyer analysis. The OST among different groups was compared using the Bonferroni test after the log-rank test. *; $P<0.05$ vs no hypoglycemia and success of respiratory compensation.

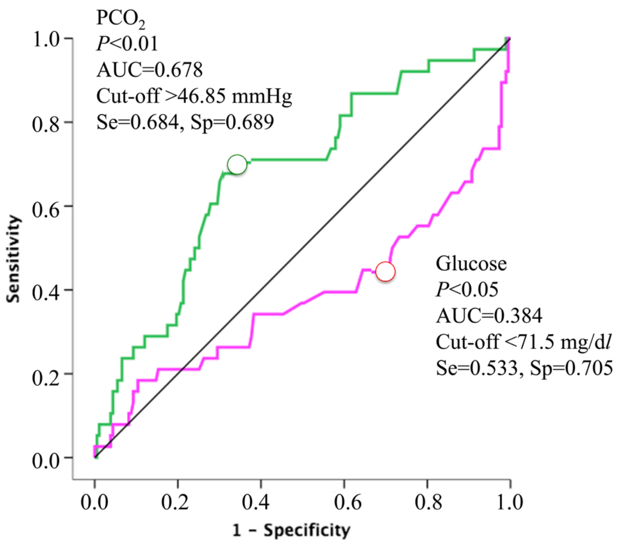

Fig. 2. ROC curves for partial pressure of carbon dioxide and serum glucose concentration for non-survival progression of diarrheic calves. The optimal cut-off point for the test was calculated by the Youden index (J). Open Circle: Cut-off point.

The i-STAT Portable Clinical Analyzer, a point-of-care testing has been shown to be valuable in the early diagnosis and management in critically ill patients [1]. Previous studies demonstrated that agreement between i-STAT Portable Clinical Analyzer for point-of-care testing with standard laboratory testing in the analysis of electrolytes, glucose, blood pH and gases was goods [1, 20]. In addition, i-STAT portable clinical analyzer performed similarly to the standard clinical laboratory systems for evaluation of glucose concentrations in horses [11]. Therefore the laboratory findings in this survey were valid.

In this survey, we adopted cut-off value for hypoglycemia of diarrheic calves was set at <68.0 mg/d*l* [15]. Large-scale epidemiology investigation demonstrated that plasma glucose concentration of non-survival diarrheic calves (median: 72.1 mg/d*l*) were significantly lower than those of survival diarrheic calves (median: 79.3 mg/d*l*) [30]. In addition, our present survey proposed diagnostic cut-off point for plasma glucose concentration for non-survival progression of diarrheic calves was set at <71.5 mg/d*l*. Furthermore previous study adopted similar reference range (79.3–124.3 mg/d*l*) for diarrheic calves with hypoglycemia [29]. Therefore it seems that the cut-off value that we adopted is appropriate to diagnose hypoglycemia.

Trefz *et al*. [29] previously reported that hypoglycemia was associated with a poor survival rate in calves. Furthermore, Tennant *et al*. [26] found that diarrheic calves with severe hypoglycemia (less than 40 mg/d*l*) were almost always extremely dehydrated. Based on hematocrit (P=0.08) and hemoglobin (P=0.08) concentrations, the non-survival group tended to become dehydrated more often than the survival group in this survey. Dehydration causes anaerobic metabolism, decreasing tissue oxygen levels and decreased glucose oxidation, resulting in anaerobic metabolism and inefficient utilization of glucose [17]. Indeed, the addition of glucose to IV fluid solutions is widely used to provide energy [6], but it is important to improve the glucose efficiency to correct dehydration in diarrheic calves.

Hypoglycemia has been reported in diarrheic calves that were weak, lethargic, or comatose [26] and usually occurs in the terminal stages of the disease [16]. The mean fecal fat content was higher in calves with diarrhea than in healthy calves, and the mean caloric uptake from milk was decreased by 31% in diarrheic calves compared with healthy calves. Thus, the negative energy balance continues [33]. In addition, recent studies demonstrated that diarrheic calves developed severe proteolysis and lipolysis [9, 31]. This suggests that diarrheic calves need to more energy for maintenance because malnutrition is serious in diarrheic calves with hypoglycemia [29]. As malnutrition causes marked physiological and metabolic changes, malnourished animals respond poorly to treatment. Treatment or prevention of hypoglycemia and hypothermia, and correction of micronutrient deficiencies are the main topics in the WHO guidelines for the management of severe malnutrition [32]. Similarly, IV infusion in diarrheic calves should contain glucose in addition to amino acids and lipids, but there is very little research on providing nutritional support to diarrheic calves. Parenteral nutrition (PN) has been widely adopted in human care since the late 1960's [10]. PN has been used for patients with inappropriate oral feeding or any medical condition that leads to gastrointestinal failure. PN is usually composed of a dilute solution of amino acids, glucose, and micronutrients. Therefore, greater concentrations of nutrients can be provided. Moreover, PN infusion therapy may be useful for treatment of diarrheic calves exhibiting negative energy balance compared with classical glucose solution therapy.

In general, respiratory compensation of metabolic disorders occurs rapidly. Patients with metabolic acidosis have a base excess value of zero, usually due to compensatory respiratory alkalosis [4]. The functional capacity of respiratory compensation of acidotic disorders in calves was reported around the same time as for humans [7]. In this survey, multivariate logistic regression analysis demonstrated that diarrheic calves with failure of respiratory compensation have a poor prognosis. However, we only selected diarrheic calves with no concurrent severe disorders such as pneumonia or bronchitis. One reason for the failure of respiratory compensation in calves may be severe dehydration [7]. We proposed a diagnostic cut-off point for PCO_2 for non-survival progression of diarrheic calves, and multivariate logistic regression analysis using the cut-off values for PCO_2 resulted in a higher OR than when using the previous value. Respiratory compensation likely causes respiratory alkalosis in calves with metabolic acidosis, thus it may be necessary to set a lower value for PCO_2. However, there are few studies on respiratory compensation in calves with metabolic acidosis [7]. Our data may be useful for respiratory compensation in calves with metabolic acidosis.

We found that hypoglycemia and failure of respiratory compensation were the major risk factors associated with a negative outcome in diarrheic calves. In diarrheic calves, treatment seems to be unsuccessful when ventilatory deficiency occurs. The IV fluid therapy for the diarrheic calves with or without hypoglycemia in the initial examination, there were no significant differences in the volume of the total fluid (4,513.7 ± 1,530.8 vs 4,479.8 ± 1,464.8 m*l*, P>0.05), 7.0% sodium bicarbonate solution (440.8 ± 184.0 vs 396.6 ± 197.0 m*l*, P>0.05), glucose (91.9 ± 66.3 vs 77.6 ± 59.8 g, P>0.05), and glucose per total fluid volume (2.0 ± 1.3 vs 1.8 ± 1.5%, P>0.05) between groups, respectively. As we have demonstrated, it seems that veterinarians paid no attention to hypoglycemia. However, as hypoglycemia has a higher risk of death, diarrheic calves with hypoglycemia require more careful medical attention during their recovery from diarrhea and need nutritional management for treatment to progress appropriately.

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