



## NOTE

Internal Medicine

## Advantage of parenteral nutrition for diarrheic calves

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**ABSTRACT.** This study assessed the advantages of dextrose and amino acid mixture solution as parenteral nutrition (PN) therapy for diarrheic calves. Thirty diarrheic calves were randomly assigned to receive PN (PN group, n=15) or only dextrose solution (Dex group, n=15). The treatment period for the PN group (4.0 days; min-max, 2–10 days) was significantly shorter than that for the Dex group (6.0 days; min-max, 3–21 days) ( $P<0.01$ ). The PN therapy tended to improve plasma diamine oxidase activity compared with traditional therapy. One potential association between PN therapy and shortened treatment period may be the repair of damaged intestinal villi. Although our proposal has limitations, PN therapy suggested the potential for new treatment of diarrheic calves.

**KEY WORDS:** amino acid, calf, cryptosporidiosis, diarrhea, supportive therapy

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Infectious diarrhea remains one of the biggest health challenges in both the beef and dairy industries, and has a significant impact on economic productivity [6]. *Cryptosporidium parvum* (*C. parvum*) is one of the most commonly isolated gastrointestinal pathogens from dairy calves with mucosal inflammation and malabsorptive diarrhea [16, 20, 28]. Malabsorptive diarrhea leads to overall absorption of not only electrolytes and water, but also decreases carbohydrates, lipids, and amino acids in calves [7]. Furthermore, persistent anorexia accelerates the negative energy balance during the diarrheic period [27]. Therefore, providing nutrients that facilitate repair of the damaged intestine and prevent negative energy balance is one of the main principles of ancillary treatment in neonatal calves with diarrhea [4].

The addition of dextrose to intravenous (IV) fluid solutions is widely used to provide energy to diarrheic calves [2]. The supply of dextrose maintains the glycometabolism and inhibits increases in beta-hydroxybutyrate (BHBA) caused by lipolysis. Lund *et al.* [17, 18] reported that the addition of dextrose to IV fluid solutions does not prevent proteolysis in patients with abdominal surgery. In addition, the infusion of dextrose prevented the rise in levels and uptake of BHBA, but high release of several individual amino acids was observed [17]. Therefore, the addition of dextrose to IV fluid solutions is useful for preventing lipolysis, but may accelerate utilization of plasma amino acids.

Parenteral nutrition (PN) has been widely used for humans since the late 1960's and represents a major advancement in improving the quality of care for patients with gastrointestinal tract disorders [3]. PN is usually composed of a dilute solution of amino acids, dextrose, and micronutrients. Amino acid administration helps to prevent intraoperative metabolic changes in humans [10, 14]. Acute (3–5 hr) amino acid infusion in humans has been reported to decrease protein breakdown in skeletal muscle and splanchnic tissue [11, 23]. The most critical component of nutritional therapy is the protein component because maintenance of lean body mass is central to nutritional support [8]. PN infusion therapy containing amino acids is likely useful for facilitating repair of the damaged intestine and preventing negative energy balance in diarrheic calves, but there are few articles on the usefulness of PN infusion for calves. Therefore, the aim of our studies was to evaluate the advantages of PN therapy for treatment of calves with diarrhea, using typical dextrose solution therapy with DAO activity as an index.

All procedures were performed in accordance with the guidelines for Care and Use of Laboratory Animals of the School of Veterinary Medicine at Rakuno Gakuen University and the National Research Council [21]. Thirty diarrheic calves (seven Holstein male, eleven Holstein female, five first filial generation of a Japanese Black male, one first filial generation of a Japanese Black

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**Table 1.** Composition of Unicaliq-L solution and 15% dextrose solution in PN and Dex groups

|           | Total free amino acid (g) | BCAA content ratio (%) | Dextrose (g/dl) | Non protein calorie (kcal) | Total calorie (kcal) |
|-----------|---------------------------|------------------------|-----------------|----------------------------|----------------------|
| PN group  | 25.03                     | 31.00                  | 12.5            | 500.0                      | 600.0                |
| Dex group | -                         | -                      | 15.0            | 600.0                      | 600.0                |

PN group: Unicaliq-L solution, Dex group: 15% dextrose solution.

female, one Japanese Black male and five Japanese Black female) with a mean age of  $11.9 \pm 5.8$  days (from 5 to 37 days old) were enrolled in this study. All calves were referred to the Minami Hokkaido Agricultural Mutual Relief Association to treatment diarrhea between January 2016 and March 2016. In these calves, duration of diarrhea was unknown. In twenty-six of 30 calves (86.7%), *C. parvum* was detected using a *C. parvum* rapid test kit (BOX-BIOK-155-10 Test, Cosmo Bio Co., Ltd., Tokyo, Japan) [25]. The remaining four calves were diagnosed as negative. The calves presented diarrhea and mild metabolic acidosis diagnosed by physical examination and blood gas analysis (i-STAT 1, Abbott Lab., IL, U.S.A.), in which intravenous fluid therapy to correct dehydration, electrolyte status, and negative nutritional status was needed. All of the calves examined were offered two feeding occasions per day with whole milk at a rate of 5% body weight per feed in the morning and afternoon; they also had ad libitum access to hay and water, but not concentrated feed throughout the study period.

Commercially available PN solution composed of branched-chain enriched amino acids and dextrose for human use (The Unicaliq-L solution, Terumo Co., Ltd., Tokyo Japan), and 15% dextrose solution (Dex) were used in this study. The calorie content of these infusions was adjusted to 600 kcal. The compositions of the PN and Dex solutions are detailed in Table 1. All calves received 3,000 ml of acetate Ringer's solution for rehydration at a flow rate of 20 ml/kg/hr. After that, calves received either 1,000 ml of the PN (PN group, n=15) or Dex solutions (Dex group, n=15) as a nutritional treatment over 2 hr for once per day, and lasted for maximum second treatment day; If depression (ataxia and coma) or anorexia (leave the milk at the rate of 5% of body weight per feeding) still present in second treatment day, calves received the same nutritional treatment as initial treatment. However, when depression or anorexia recurred after 2 days from initial treatment day, calves received extra intravenous fluids, not including nutritional fluid solution, to correct dehydration and metabolic acidosis. All diarrheic calves also received the same supportive therapy in initial treatment; intramuscular administration of oxytetracycline (Terramycin LA, Zoetis Japan Co., Ltd., Tokyo, Japan) at a dose of 20 mg/kg and subcutaneous administration of meloxicam (Metcam, Kyoritsu Seiyaku Co., Ltd., Tokyo, Japan), including nonsteroidal anti-inflammatory drug (NSAID) agents, at a dose of 0.5 mg/kg. After that, all calves received only mloxicam every 3 days, except fluid therapy, as a supportive therapy throughout the treatment period. The duration of treatment depended on whether depression and anorexia were still present and if fecal characteristics returned to normal. A 14-gauge catheter (Sureflow Catheter SR-OT1464C, Terumo Co., Ltd., Tokyo, Japan) was placed into the right jugular vein for fluid infusion. Venous blood samples were anaerobically collected in both a heparinized 1-ml syringe and non-heparinized 5-ml syringe from the left jugular vein immediately before fluid infusion (pre), immediately after completely finishing the fluid infusion (post), and 24 hr after the initiation of fluid infusion.

The fecal status in initial treatment was assessed using a scoring system (0: firm, 1: pasty, 2: loose, and 3: watery) as described elsewhere [13]. Heparinized blood samples were analyzed for blood gases (i-STAT 1, Abbott Lab., Princeton, IL, U.S.A.). Non-heparinized blood samples were stored in EDTA-2K-coated vacuumed tubes and then centrifuged for 15 min at 3,000 rpm with a standardized procedure to harvest plasma. Free amino acid concentrations in plasma were next measured by high-performance liquid chromatography (HPLC) using a commercial amino acid analysis kit (EZ: faast, Shimadzu, Kyoto, Japan) and automated amino acid analysis system (The Shimadzu Prominence and LCMS-2020, Shimadzu). The total amino acids (TAA: Threonine + Valine + Methionine + Isoleucine + Leucine + Phenylalanine + Histidine + Lysine + Arginine + Tryptophan + Serine + Glutamic acid + Glycine + Alanine + Tyrosine + Proline + Aspartic acid + Asparagine + Glutamine + Cysteine-Cysteine) and BCAA (Valine + Leucine + Isoleucine) were calculated. DAO activity in plasma was also measured by ELISA using a commercial DAO ELISA kit (Bovine Diamine Oxidase ELISA kit, My BioSource, San Diego, CA, U.S.A.). In addition, data were collected to determine whether early infusion of PN affected the treatment period.

The data are expressed the means  $\pm$  standard deviation (SD) and non-normally distributed data are expressed as medians and ranges. The treatment periods were compared between groups using Mann-Whitney *U*-test. We processed plasma amino acids concentrations and plasma DAO activity for each dependent variable (treatments and times) with two-way repeated measures ANOVA. If interaction was found, measured dependent variables were compared between and within groups for each sample collection period using the student's *t*-test or Mann-Whitney *U*-test after the *F*-test and Bonferroni test, respectively. The significance level was  $P < 0.05$ .

The PN and Dex groups consisted of fifteen diarrheic calves (three Holstein male, five Holstein female, three first filial generation of a Japanese Black male, one Japanese Black male and three Japanese Black female) with a mean age of  $11.8 \pm 3.9$  days (from 7 to 19 days old) and fifteen diarrheic calves (six Holstein male, four Holstein female, two first filial generation of a Japanese Black male, one first filial generation of a Japanese Black female and two Japanese Black female) with a mean age of  $11.9 \pm 7.4$  days (from 5 to 37 days old), respectively. Fecal scores in the PN and Dex groups were 3.0 (min-max, 1–3) and 2.0 (min-max, 1–3), respectively. No significant differences were observed in fecal scores between the PN and Dex groups, and none of the calves had bloody stool. In each group, thirteen of 15 calves (86.7%) *C. parvum* was detected, respectively. All calves presented with mild dehydration (a slight separation of the third eyelid from the orbit) and central nervous symptoms, such as ataxia and coma, at pre.

**Table 2.** Blood gas and plasma free amino acids analysis in this study

|                          |         | Pre<br>(n=11)   | Post<br>(n=11)                | 24 hr<br>(n=11) |
|--------------------------|---------|-----------------|-------------------------------|-----------------|
| pH                       | PN      | 7.23 ± 0.08     | 7.25 ± 0.05                   | 7.27 ± 0.05     |
|                          | Dex     | 7.24 ± 0.06     | 7.26 ± 0.07                   | 7.28 ± 0.06     |
| BE                       | (mM) PN | -6.2 ± 6.8      | -4.3 ± 4.3                    | -2.3 ± 3.9      |
|                          | Dex     | -5.4 ± 4.6      | -3.8 ± 5.1                    | -1.1 ± 4.5      |
| TAA <sup>a)</sup>        | (nM) PN | 2,665.1 ± 502.2 | 2,968.5 ± 946.5*              | 2,432.4 ± 438.4 |
|                          | Dex     | 2,861.4 ± 451.4 | 1,938.0 ± 415.6 <sup>b)</sup> | 2,471.1 ± 419.5 |
| BCAA <sup>a)</sup>       | (nM) PN | 468.1 ± 97.0    | 678.9 ± 180.4 <sup>b)</sup>   | 379.8 ± 66.4    |
|                          | Dex     | 573.6 ± 78.6    | 388.5 ± 108.8 <sup>b)</sup>   | 428.4 ± 81.2    |
| Valine <sup>a)</sup>     | (nM) PN | 223.1 ± 51.3    | 316.3 ± 59.4 <sup>b)*</sup>   | 181.8 ± 40.2    |
|                          | Dex     | 269.6 ± 40.8    | 207.1 ± 55.4 <sup>b)</sup>    | 202.6 ± 46.2    |
| Leucine <sup>a)</sup>    | (nM) PN | 140.4 ± 32.1    | 210.3 ± 72.7 <sup>b)*</sup>   | 114.1 ± 18.8    |
|                          | Dex     | 172.5 ± 30.9    | 105.8 ± 38.7 <sup>b)</sup>    | 127.0 ± 24.1    |
| Isoleucine <sup>a)</sup> | (nM) PN | 104.7 ± 21.7    | 152.2 ± 56.1 <sup>b)*</sup>   | 84.0 ± 16.7     |
|                          | Dex     | 131.6 ± 29.6    | 75.7 ± 21.0 <sup>b)</sup>     | 98.9 ± 20.9     |

Mean ± SD, PN; PN group, Dex; Dex group. a) Significant difference ( $P < 0.01$ ) was observed in interaction between treatment and time by two-way repeated measures ANOVA. b) vs pre  $P < 0.01$  by Bonferroni test. \* vs Dex group  $P < 0.01$  by student's *t*-test or Mann-Whitney *U*-test after the *F*-test.

One of fifteen (6.7%) calves that received nutrition fluid using PN and two of fifteen (13.3%) calves that were nutritionally managed with Dex alone died, but this difference is not significant. The treatment period for the PN group (4.0 days; min-max, 2–10 days) was significantly shorter than that for the Dex group (6.0 days; min-max, 3–21 days) ( $P < 0.01$ ).

The results of the blood analysis are summarized in Table 2. Based on blood gas analysis at pre, calves in the PN (pH:  $7.23 \pm 0.08$ , BE:  $-6.2 \pm 6.8$  mM) and Dex groups ( $7.24 \pm 0.06$ , BE  $-5.4 \pm 4.6$  mM) were diagnosed with mild metabolic acidosis. Metabolic acidosis in calves that received PN or Dex was restored at 24 hr after initiation of fluid infusion because blood pH and BE in PN ( $7.27 \pm 0.05$  and  $-2.3 \pm 3.9$  mM) and Dex ( $7.28 \pm 0.06$  and  $-1.1 \pm 4.5$  mM) groups were slightly increased by fluid therapy. However, in the PN and Dex groups, 4/15 and 6/15 calves, respectively, exhibited depression or anorexia at 24 hr after initiation of fluid infusion. Therefore these calves received their respective nutritional treatment for one more day.

The plasma amino acids analysis was conducted in twenty-two of 30 calves. In each groups consisted of 11 calves, and included one of 11 calves without *C. parvum* infection, respectively. Based on the repeated measures ANOVA, the variation of plasma TAA concentration statistics showed that significant difference was observed only interaction between treatment and time ( $P < 0.01$ ). The plasma TAA concentration in the Dex group at post ( $1,938.0 \pm 415.6$  nM) was significantly decreased compared with at pre ( $2,861.4 \pm 451.4$  nM). Although there were no significant differences in the concentration of TAA in the PN group at post ( $2,968.5 \pm 946.5$  nM), it was slightly increased compared with the pre value ( $2,665.1 \pm 502.2$  nM). Therefore, the plasma TAA concentration at post was significantly different between the PN and Dex groups ( $P < 0.01$ ). However, these differences were lost by 24 hr after the initiation of fluid therapy. The variations of plasma concentrations of BCAA (valine, leucine and isoleucine) statistics by repeated measures ANOVA revealed significant difference in time ( $P < 0.05$ ) and interaction between treatment and time ( $P < 0.01$ ), respectively. The plasma BCAA concentration in the Dex group at post ( $388.5 \pm 108.8$  nM) was significantly decreased compared with at pre ( $573.6 \pm 78.6$  nM). The plasma BCAA concentration in the PN group at post ( $678.9 \pm 180.4$  nM) was significantly increased compared with at pre ( $468.1 \pm 97.0$  nM). The plasma BCAA concentration at post was significantly different between the PN and Dex groups ( $P < 0.01$ ). Like variation of plasma TAA concentration, these differences were lost by 24 hr after the initiation of fluid therapy. The plasma TAA and BCAA concentration in the PN group at post seems to depend on infusion product. In addition, all calves received 4,000 ml of solution for rehydration and nutritional treatment. There is no denying that the plasma TAA and BCAA concentration in the Dex group at post could be due to being diluted, not only Dex solutions effects. At 24 hr after the initiation of fluid therapy, there were no significant differences in plasma TAA or BCAA in either group, and the values were restored to pre values. The plasma TAA and BCAA concentrations in the PN group at 24 hr after initiation of fluid therapy may have returned to pre values could have been excreted or utilized for energy. The plasma concentrations of TAA and BCAA at 24 hr after the initiation of fluid therapy in the Dex group also returned to pre values. In this study, we cannot ascertain difference in change between post and 24 hr after initiation of fluid therapy from plasma amino acid variations.

Several researchers demonstrated that diamine oxidase (DAO) is a cytoplasmic enzyme found primarily in the villus epithelial cells of the small intestine that plays a crucial role in the degradation of histamine in the small intestine [15, 24]. DAO is well known as a serum biomarker for intestinal mucosal injury (IMI) [1]. According to previous reports, the changes in serum DAO activity indicate that the intestinal barrier is damaged [1, 9]. The plasma DAO activity was measured in eighteen of 30 calves in this study. In each groups consisted of 9 calves, and included one of 9 without *C. parvum* infection, respectively. The plasma DAO activity in the PN and Dex group at pre were  $124.2 \pm 54.4$  and  $104.1 \pm 61.7$  IU/ml, respectively. After nutritional treatment therapy, plasma DAO activity in the PN and Dex groups changed to  $171.2 \pm 67.7$  and  $125.6 \pm 52.8$  IU/ml, respectively. Based on the repeated measures ANOVA, there were significant trend in treatment ( $P = 0.10$ ) and time ( $P = 0.07$ ), but no significant difference

was observed in interaction between treatment and time ( $P>0.10$ ). It was suggested that variations of plasma DAO activity in PN and Dex groups observed at post tended to be larger in PN group than those of Dex group, but no clear difference was observed. However, the DAO activity in 9/9 PN and 5/9 Dex calves were increased compared with the pre values until the end of fluid infusion. Although our proposal has limitations, using plasma DAO activity as an index, post-treatment findings of calves receiving PN and Dex therapy in this clinical study suggest the PN have possibilities for new treatment of diarrhetic calves. One potential association between PN therapy and shortened treatment period is the repair of damaged intestinal villi. Administration of glutamine and arginine accelerates intestinal mucosal regeneration in animals [5, 12]. In addition, amino acids play an important role in vital responses such as important nutrient signals [19] and immunity [22]. Several researchers demonstrated the utility of long or short-term amino acid administration in patients with nutritional imbalance [14, 26]. Our results suggested that maintenance of the nutritional condition is improving treatment, especially due to regenerative effect of damaged intestinal villi. In conclusion, providing short-term PN therapy may aid in reducing the treatment periods for calves with diarrhea. This treatment regimen may be beneficial for clinical use in calves with diarrhea. Future studies to examine the prescription of PN infusion solution with an amino acid ratio suitable for calf diarrhea are needed.

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