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NOTE

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Accuracy of the point-of-care glucose meter for use in calves

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ABSTRACT. The aim of this study was to evaluate the accuracy and precision of portable blood glucose meters, such as i-STAT 1 and Precision Xceed, for use in calves. Whole blood and plasma samples were obtained from eleven calves that received 2.5 or 5.0% dextrose-containing polyelectrolyte isotonic solutions. Measurements using the i-STAT 1 (r^2=0.99, P<0.0001) and Precision Xceed (r^2=0.96, P<0.0001) were well correlated with those by the hexokinase method, which is the gold standard. Although the accuracy of i-STAT 1 was equivalent to that of the hexokinase method, there was an autocorrelation in the residuals between the results from the Precision Xceed and the hexokinase method. Thus, the i-STAT 1 can be used to measure the blood glucose concentration in cattle.

KEY WORDS: accuracy, cattle, cow-side test, glucose, portable blood glucose meter

Diarrhea is one of the most common diseases in the clinical setting, and it can cause hypoglycemia in calves [17]. Diarrheic calves with hypoglycemia have severe malnutrition [20] that usually occurs in the terminal stages of the disease [10]. Malnourished animals respond poorly to treatment because of marked physiological and metabolic changes [21]. As hypoglycemia has a higher risk of death in diarrheic calves, it is important to immediately evaluate the blood glucose concentration to detect hypoglycemia requiring treatment [9, 19, 21].

Polyelectrolyte isotonic solutions with 2.5 to 5.0% dextrose are widely used in fluid therapy for cattle [2, 16], especially for hypoglycemic calves with diarrhea. However, the large volume of glucose supplemented during fluid replacement increases the risk of developing hyperglycemia. In particular, hyperglycemia due to fluid therapy causes extreme rebound hypoglycemia [9], and negatively impacts abomasal motility and function [6]. It is important to measure the blood glucose concentration during infusion for appropriate fluid therapy management [9, 19].

It is well known that endotoxemia in cattle affects the blood glucose concentrations depending on the pathological condition. In general, endotoxemia initially results in transient hyperglycemia that may be followed by marked hypoglycemia in the terminal stages [17]. As stress hormone and inflammatory cytokine signaling induces peripheral insulin resistance over time, inflammation of endotoxemia usually causes hyperglycemia [7]. Acute lipopolysaccharide (LPS) exposure was suggested to reduce the expression and activity of rate-limiting enzymes in glucose production [15]. Furthermore, LPS may enhance the effects of co-delivered insulin, precipitating hypoglycemic shock within 1–2 hr of challenge [7]. Therefore, managing blood glucose levels at the farm, referred to as the "Cow-Side-Test (CST)", is advantageous for the diagnosis and treatment of hypoglycemic and hyperglycemic cows.

Most automated chemistry analyzers (ACA) measure the glucose concentration by means of a hexokinase or glucose oxidase method as the gold standard, but potential disadvantages include blood sample volume requirements and slow turnaround time [8]. Glucose meters for self-monitoring of blood glucose (SMBG) is an essential device for the management of ambulatory and hospitalized diabetes patients. These hand-held glucose meters are used in veterinary practice as portable blood glucose meter (PBGM). In the other hand, point-of-care (POC) analyzers that require minimal blood samples and that can measure a wide range of other variables including glucose concentration rapidly also categorized as CST in bovine practice. Recently, many new PBGM from several manufacturers have appeared on the market. PBGM used for humans are low in cost and widely used, and have become useful devices for outpatient clinical care for diabetes patients [1, 11, 12]. The basic operation of commercially available PBGM and POC analyzer is the same, with blood drawn into the reaction chamber of the test strip by capillary action

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and the blood glucose concentration is measured by an electrochemical or photometric method [5, 8]. As PBGM and POC analyzer designed for veterinary practice are not commercially available in Japan, it is unclear whether they can be used in cattle practice. A previous study [5] reported that the difference in glucose distribution between red blood cells and plasma depending on the animal species leads to inaccurate glucose values measured by glucose meters designed for humans.

PBGM are used to evaluate venous and capillary blood glucose concentrations in dogs and cats [22]. However, there were significant differences in the accuracy of PBGM when used to measure the blood glucose concentration in dogs [4]. This suggested the importance of using the same device for monitoring trends in dogs and using an instrument-specific reference range [8].

There are few reports on whether PBGM for humans can be applied to ruminants and camels. Accuracy trials for alpacas and juvenile white-tailed deer suggested that the available PBGM and POC analyzer are not appropriate for measuring blood glucose concentrations because they are not equivalent to laboratory analyzers [3, 19]. Although measurements by PBGM for humans strongly correlate with those by the reference method, the glucometer overestimated the values in dairy cattle at higher-than-physiological glucose concentrations (>5.2 mmol/*l*) [23]. Thus, quality assurance and precision testing for each device is required for use in cattle.

The purpose of this study was to evaluate the accuracy and precision of i-STAT 1 and Precision Xceed (Abbott Lab, Princeton, IL, U.S.A.), two commercially available PBGM and POC analyzer for humans use, by comparing the results with these meters with those by ACA using a reference method based on the hexokinase reaction.

All procedures were performed in accordance with the Good for the Care and Use of Laboratory animals of the school of Veterinary Medicine at Rakuno Gakuen University (Approved #:VC15H21) and the National Research Council [13]. Eleven calves kept at Rakuno Gakuen University Veterinary Teaching Hospital were enrolled in this study. The quality of i-STAT 1 (Abbot Lab) was evaluated first, and the accuracy of the Precision Xceed was assessed using different cows.

Seven calves (125.8 ± 10.8 kg) were randomly allocated to receive 40 m*l*/kg of isotonic acetate Ringer's solution or 120 m*l*/kg of acetate Ringer's solution with 5% dextrose via the jugular vein for two hours. Blood samples (total 96) were collected via indwelling jugular catheter before infusion, and at 0.5, 1, 2, 3, 4, 6, and 24 hr. Blood glucose concentrations in whole blood samples (95 *μl)* were measured using i-STAT 1 and its cartridge (i-STAT EC8+ Cartridge, Abbott Lab). The limits of quantification of the glucometer according to the test strip package insert are 20–700 mg/d*l*.

Four calves (101.2 ± 61.3 kg) received 20 m*l*/kg of hypotonic Ringer's solution with 2.5% dextrose intravenously (IV) at a flow rate of 10 m*l*/kg/hr, and blood samples were taken before, and at 15, 30, 45, 60, 75, 120, 180, and 300 min after fluid infusion. Whole blood sample were taken from the contra lateral jugular vein via catheter for measuring glucose concentration both of PBGM and standard method, respectively. The drop of blood was applied directly to the end of a test strip from syringe. The Precision Xceed provided results in approximately 5 sec. The limits of quantification of the glucometer according to the test strip package insert are 20–500 mg/d*l*.

Immediately after measuring whole blood glucose concentrations by the i-STAT 1 or Precision Xceed, 5 m*l* blood samples were stored in vacuum tubes with the preservative sodium fluoride (Venoject II, Terumo Co., Tokyo, Japan) [14], and the tubes were then gently inverted 10 times to ensure thorough mixing with the preservative and placed in a chilled container. Plasma was separated by centrifugation at 3,000 rpm for 15 min at room temperature and stored at −80°C until analysis. All plasma glucose concentrations were measured at the Animal Health Laboratory (Fuji film Monoris Japan, Tokyo, Japan) using a commercial reagent kit (N-assay Glu-UL, Nittobo Medical Co., Ltd., Tokyo, Japan) for an ACA (AU 480, Beckman Coulter Inc., Brea, CA, U.S.A.).

Non-normally distributed data were expressed as the median and ranges. Data were statistically analyzed using the SPSS software program (ver.23. IBM Japan, Tokyo, Japan). Glucose concentrations measured by the hexokinase method were considered the reference values in all analyses. The Pearson product-moment correlation coefficient was used to assess the strength and direction of association between any two assays measured on an interval scale. Linear regression model analysis was also performed. Durbin-Watson statistics and Bland-Altman plot were used to assess the residuals between the results from the two devices and the laboratory tests. To assess accuracy, two glucose meters values and reference values were compared using Wilcoxon's test. The significance level was set at $P<0.05$.

Eleven out of 96 samples evaluated using the i-STAT 1 were excluded from statistical analysis because they exceeded the measurement limit. Pearson correlations between the glucose concentrations by the reference method and 2 devices are shown in Fig. 1. The results by the i-STAT 1 correlated well with those by the reference method ($r^2=0.99$, $P<0.0001$). The relationship based on linear regression analysis was as follows: glucose concentration (mg/d*l*, i-STAT 1)=1.02 × glucose (mg/d*l*, ACA) + 2.31. According to Durbin-Watson statistics, there was no autocorrelation in the residuals of the measurement results between the i-STAT 1 and the reference method ($P=0.05$). Plotting of the residuals between the i-STAT 1 and ACA results against their means revealed that the glucometer readings were, on average, 6.17 mg/d*l* higher. Overall, 94% of the observations were between the 95% confidence intervals in the Bland-Altman plot, indicating good agreement. The median blood glucose concentration detected by the i-STAT 1 and the reference method was 97 (58–689) mg/d*l* and 94 (55–676) mg/d*l*, respectively. Based on Wilcoxon's test, the ability of i-STAT 1 to measure blood glucose was not significantly different from that of the laboratory assay ($P>0.05$).

The measurements by Precision Xceed correlated well with those by the reference method ($r^2=0.96$, $P<0.0001$). The relationship based on linear regression analysis was as follows: glucose concentration (mg/d*l*, Precision Xceed)=1.32 × glucose (mg/d*l*, ACA) + 10.68. Using Durbin-Watson statistics, an autocorrelation was detected in the residuals between the Precision Xceed glucose meter and the laboratory test ($P>0.05$). Plotting of the residuals between the Precision Xceed and ACA results against their means revealed that the glucometer readings were, on average, 31.59 mg/d*l* higher. Overall, 93% of the observations were between the 95% confidence intervals in the Bland-Altman plot, indicating good agreement. The median blood glucose concentration detected by the

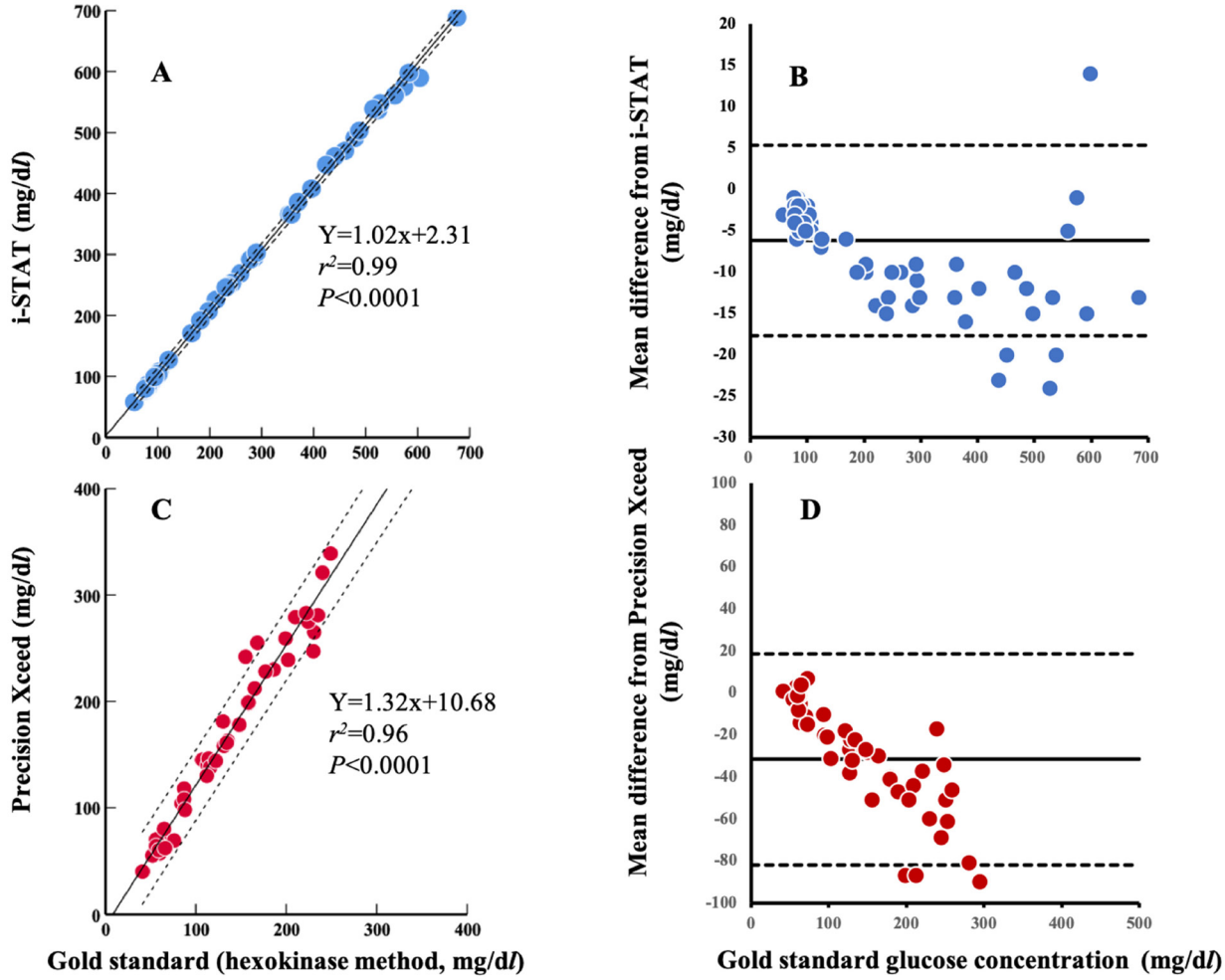

Fig. 1. Person's correlation coefficients among the i-STAT 1 (A), Precision Xceed (C), and hexokinase method as the gold standard for blood glucose concentrations. Bland-Altman plot of glucose concentrations measured by the i-STAT 1 (B) or Precision Xceed (D). The solid line represents the mean difference between the 2 methods and the 95% confidence limits are indicated by the dashed lines.

Precision Xceed and reference method was 152 (40–339) mg/d*l* and 126 (41–249) mg/d*l*, respectively. Based on Wilcoxon's test, the ability of Precision Xceed to measure blood glucose is not significantly different from that of the laboratory assay ($P>0.05$).

Currently, most portable blood glucose meters are easy to affected by the relative plasma volume, partial pressure of oxygen (pO_2), and blood pH [5]. Previous report showed that 2.5% dextrose-containing polyelectrolyte isotonic solution increased relative plasma volume during the administration but did not change in arterial pH and serum electrolyte [18]. In this study, we used 2.5 or 5.0% dextrose-containing polyelectrolyte isotonic solutions in order to make various glucose concentration. Although detailed data on factors that influence the measurement could not be shown, it was considered that interference was small. In this study, we investigated the accuracy of blood glucose measurement by the two most popular POC analyzer and PBGM. We found a high correlation between glucose values measured by the i-STAT 1 and the hexokinase method, which is the gold standard. Therefore, the i-STAT 1 can be used to measure blood glucose concentrations in cattle as CST because the i-STAT 1 and ACA produced equivalent results. In contrast, an autocorrelation was detected in the residuals between the results from Precision Xceed and the ACA. However, the results by Precision Xceed were highly correlated with those by the reference method and it can measure blood glucose concentration with the same accuracy as the reference method. At higher blood glucose concentrations, Precision Xceed overestimated the values. PBGM are calibrated to show venous-equivalent concentrations by using built-in conversion factor. Inconsistent under- and overestimation of glucose concentration in hypo- or hyperglycemic samples was detected in a commercial PBGM in dogs and alpacas' studies [4, 5, 19]. In this study, proprietary glucometer correction algorithm in Precision Xceed may have resulted in a greater degree of error in the glucose concentration in the hyperglycemic range. In description of Precision Xceed manual, peripheral whole blood is recommended to use for measuring glucose concentration. However, it is difficult to obtain capillary whole blood without removing fur hair in animal. Venipuncture site including the jugular, auricular, and coccygeal vein is most commonly used for blood collection in bovine practice. Moreover, the use of venous blood collection have advantage over the capillary whole blood because the former is available to other measurement. Therefore, venous whole blood sample was used in

this study. A previous report suggested that it is easier to clinically compensate for PBGM that consistently overestimate the glucose concentration within a specific range (proportional bias) than PBGM where the direction of error relative to a reference method is random and unpredictable [5]. Thus, the Precision Xceed may be able to be used for CST assuming that the measured blood glucose concentrations are higher than those by the reference method.

In conclusion, there were significant differences in the accuracy of POC analyzer and PBGM when used to measure the blood glucose concentration in calves. Thus, it is necessary to assess the accuracy and features of the devices. POC analyzer and PBGM are small and portable, require only a small sample, and provide results rapidly. As such, they may be a useful point-of-care tool for cattle if accuracy control tests are carried out and the features of the devices are understood.

CONFLICTS OF INTEREST. The authors declare no conflicts of interest associated with this manuscript.

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