RESEARCH PAPER

Comparison of Continuous Real Time Blood Glucose Measurement With Venous Laboratory Blood Glucose Level in Neonates During Perioperative Period

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Objective: To compare the continuous real time blood glucose (CG) measurement with venous laboratory blood glucose (LG) level in neonates during perioperative period.

Methods: Glucose levels were measured simultaneously by CG, glucometer glucose (GG) and LG at 40 time points in ten neonates during perioperative period. Intraclass correlation coefficient (ICC) and Bland Altman analysis were used for comparison.

Result: Correlation between CG and LG was excellent (ICC= 0.953; *P*<0.001), and average difference was 23.8 (95%CI 52.9 to -5.3) mg/dL, showed better reliability than at hyperglycemic state (ICC=0.653; *P*=0.006). The GG-LG showed excellent reliability with ICC = 0.985; *P*<0.001 and average difference of 15.4 (95% CI 30.7 to 0.1) mg/dL. CG at euglycemic state (ICC= 0.880; *P*<0.001).

Conclusion: CG measurement is reliable for blood sugar estimation in neonates; but has lower reliability for hyperglycemia. The continuous trend of glucose measurement by CG is helpful for timely diagnosis of hyperglycemia during perioperative period in neonates.

Keywords: *Hyperglycemia, Hypoglycemia, Surgery*.

Both hypoglycemia and hyperglycemia are dangerous to the neonatal brain [1,2]. Neonates undergoing surgery are at high risk for hyperglycemia during post-operative period and it increases the length of hospital stay [3]. Continuous glucose (CG) monitoring has the advantage of providing continuous instantaneous blood glucose level, avoiding multiple blood sampling [4]. Till date CG monitoring is not approved for blood glucose testing in routine neonatal practice. In this context, we planned to compare the blood glucose level by CG monitoring with laboratory blood glucose (LG) testing in neonates during perioperative period.

METHODS

This was a single center prospective observational study conducted over four months period in a tertiary level neonatal intensive care unit between January, 2022 and April, 2022. The study was started after approval of the institutional ethical committee, and written informed parental consent was taken prior to enrollment.

CG monitoring is a newer invasive method for blood glucose estimation in neonates with possible risk of infection and pain at insertion site. As neonates undergoing operative procedures are at high risk of hyperglycemia and remain under coverage of antibiotics and analgesics, the accuracy of this device has been tested in them.

Neonates born at term gestation (≥ 37 weeks) within 28 days postnatal age, and neonates born at < 37 weeks till discharge from hospital, were eligible for enrolment. Neonates undergoing any operative procedure under anesthesia were enrolled, and neonates with dysglycemic states (blood glucose level >150 mg/dl or < 40 mg/dL) before surgery were excluded.

Continuous glucose (CG) monitoring was measured by Free Style Libre System (Abbott), consisting of a reader and sensor kit. This device does not need repeated calibration (factory calibrated) and reading accuracy persists for two weeks [5]. The glucose value was obtained from subcutaneous tissue by an enzymatic amperometric three-electrode sensor system. After skin disinfection with ethanol swabs, the sensor was placed into the subcutaneous tissue on the lateral part of thigh or arm of the newborn, at least 2 hours prior to shifting to the operation theatre and kept for 72 hours of post-operative period. Continuous blood glucose measurement in CG reader was started one hour after the insertion of sensor. The reader was placed in a bag near the patient side and blood glucose level was recorded on hourly basis by bedside staff nurse. The sensor insertion site was frequently monitored for skin infection, and thrombophlebitis by bedside nurses and residential doctors.

The blood glucose values by bedside intermittent glucometer glucose (GG), (ACCU –CHEK Roche Diabetes Care India Pvt. Ltd.) were measured from capillary blood

samples by pricking lateral part of heel by 26G needle after proper disinfection with ethanol swabs. For laboratory estimation of blood glucose (LG), 2 mL venous blood was taken in a Sodium Fluoride container and analyzed by hexokinase method in the institutional central laboratory. GG was measured one hour prior to surgery and every six hourly during the three post-operative days as routine care. The venous sampling was done at four time points (one hour prior to surgery; at 0-2,24-26,48-50 hours of post-operative period). For the comparison, simultaneous blood glucose level measured by CG vs GG vs LG were taken for analysis. Bedside GG testing was done immediately prior to venous sampling and maximum care was taken for laboratory blood glucose estimation within 30 minutes of phlebotomy. Neonates were managed as per the blood glucose level in GG readings. The blood glucose values were mentioned as mg/dL and laboratory blood glucose (LG) is considered as reference test. Laboratory blood glucose level >150 mg/dl was considered as hyperglycemia and <40 mg/dL as hypoglycemia [6].

Assuming the minimum acceptable reliability of CG monitor Intraclass correlation coefficient (ICC)=0.8, with expected reliability ICC=0.9 and number of repetition per subjects =4; with significance level 95% and power 80%, the calculated sample size was 36. Assuming 10% drop out rate, the final sample size was 40 [7].

Statistical analysis: Continuous variables were expressed as mean (SD) and categorical variables as frequency (%). The reliability index between two different methods (CG-LG, GG-LG, CG-GG) for glucose measurement was analyzed by Intraclass correlation coefficient (ICC) [8] ICC values <0.5,0.5-0.75,0.75-0.9 and >0.9 were considered as poor, moderate, good and excellent reliability respectively. The agreement between glucose level by two different methods was also analyzed by Bland Altman analysis plot [9]. Data were analyzed by software IBM SPSS version 20.0 (IBM Corp). A *P* value <0.05 was considered to be statistically significant.

RESULT

The study included 10 consecutive neonates undergoing surgery (6 gastrointestinal surgeries, 2 neural tube defect repairs, 1 palliative surgery for complex congenital heart disease and 1 urological disorder). Simultaneous blood glucose level by CG monitoring, GG and LG were measured at 40 time points. The detail baseline characteristics of neonates are presented in **Table I**.

CG monitoring showed excellent reliability with LG (ICC= 0.953; *P*<0.001). The average difference between CG-LG was 23.8 (95% CI 52.9, -5.3) mg/dL, and 92% of the data points remained within both arms of Bland Altman analysis.

During euglycemia (27 paired observations), CG monitoring showed good reliability with LG (ICC=0.880; *P*<0.001) and the average difference between CG-LG was 19.2 (42.8, 4.4) mg/dL. However, during periods of hyperglycemia (*n*=13 paired observations), CG monitoring showed moderate reliability with LG (ICC=0.653; *P*=0.006) and average difference between CG-LG was 33.4 (64.7, 2.1) mg/dL. None of the neonates had local infection or thrombophlebitis at CG monitoring device insertion site.

The intraclass correlation coefficient between GG and LG was 0.985; *P*<0.001, the average difference between GG-LG was 15.4 (95% CI 30.7, 0.1) mg/dL in Bland Altman analysis. The average difference between CG and GG was 8.4 (95% CI 37.8, 25) mg/dL and the ICC was 0.956; *P*<0.001.

DISCUSSION

This study showed excellent reliability between CG monitoring and laboratory testing for glucose measurement in neonates. Bedside glucometer monitoring is more reliable over CG monitoring for blood sugar estimation, however CG could provide the continuous trend information.

Previous studies have demonstrated a good agreement between CG and bedside glucometer recordings in preterm neonates and more time spent in euglycemia with CG monitoring [10,11]. In another study, closed loop automated insulin delivery with CG monitor device helped in reducing dysglycemic state in preterm infants [12]. Recently the safety and feasibility of CG monitoring for detection of hypoglycemia in neonates of diabetic mothers has also been studied [13]. Historically, laboratory blood glucose has been considered as the gold standard, and bedside intermittent glucometer is used as point of care in patient management [6]. The accuracy of CG monitoring device is in congruence

Table I Baseline Characteristics of the Study Population

Characteristics	*Value*
Birth weight (g)	2228 (755)
Gestational age (wk)	34.3 (3.46)
Cesarean section[a]	6 (60)
Preterm neonates[a]	7 (70)
Male[a]	5 (50)
Age at surgery (d)[b]	19 (3,26)
Neonatal temperature (°C)	36.6 (0.2)
Time in operation theater, h	3.25 (0.75)
Blood glucose CG monitoring, mg/dL	138.55 (53.23)
GG, mg/dL	130.15 (47.89)
LG, mg/dL	114.7 (43.73)
Time gap between CG-LG, min[b]	27.5 (16, 30)

Mean values (SD), [a]no. (%) or [b]median (Q1, Q3). CG- continuous glucose; GG- glucometer glucose; LG- laboratory glucose.

WHAT THIS STUDY ADDS?

- The reliability between continuous real time glucose monitoring device and laboratory testing is excellent for glucose measurement; however, this may or may not be applicable for identifying hyperglycemia.

with previous studies, and the variation in bias level among different studies could be explained by differences in the sensor and the different glycemic ranges [14,15]. The CG monitoring device used in previous study needs frequent sensor calibration on daily basis [14]. The advanced technology in the instrument used by us provides sensor stability and eliminates repeated calibrations [5,15].

The differences between CG and LG were more during hyperglycemic states as compared to periods of euglycemia. Hence, accurate diagnosis of hyperglycemia may not be concluded from a single reading of CG monitoring device, rather trend of glucose reading may direct point of care testing or response to treatment of hyperglycemia. However, the bias in Bland Altman analysis could help in interpretation of blood glucose level from CG monitor device readings.

In perioperative neonates, the adverse effect of subcutaneous invasive electrodes of CG monitoring may be masked by co-administration of analgesics and antibiotics. The accuracy of CG monitoring during periods of hypoglycemia not evaluated in this study. Further randomized control studies are needed to explore the clinical benefit of CG monitoring for timely addressing the hyperglycemic events in neonates in postoperative period, and other high risk neonates during intensive care treatment.

The study results have applicability for neonatal population particularly extreme preterm, neonates in peri-operative period and those at risk of hyperglycemia. Our study validated the utility of CG monitoring device for glucose measurement in neonates and can be used for identification of dysglycemia during perioperative periods. Further studies and innovations in CG monitoring devices may be useful in neonatal intensive care unit in the near future.

Ethics clearance: IEC, KIMS; No. KIMS/KIIT/IEC/799/2022 dated Jan 13, 2022.
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