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Diagnosis of Hyperemesis Gravidarum in Patients with Pregnancy-Induced Vomiting Using a Point-of-Care Ketone Blood Test

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Abstract

Aim: Hyperemesis gravidarum affects 2.5% of pregnant woman and is characterized by persistent vomiting, weight loss of more than 5%, dehydration, ketonuria, and electrolyte abnormalities. Currently, there is no consensus on its definition, and there is no single, widely used set of criteria for diagnosing hyperemesis gravidarum. The aim of this study was to determine the accuracy of point-of-care ketone blood tests in diagnosing hyperemesis gravidarum.

Materials and Methods: Patients with a gestational age of <16 weeks were included and both capillary blood ketone and urine ketone levels were determined and analyzed. The diagnosis of hyperemesis gravidarum was based on two criteria: (1) persistent nausea and vomiting requiring hospitalization in the emergency department (ED) and (2) weight loss of more than 5% with nausea and vomiting.

Results: A total of 177 pregnant women with nausea and vomiting were admitted to the ED during the study period. Patients with lost files (n=73) and unsuitable gestational age (n=2) were excluded from the study. Mean gestational age was 63.1±2 days. Overall, 68.6% of the patients had emesis and 31.4% were diagnosed with hyperemesis gravidarum. The diagnostic accuracy of the point-of-care capillary blood ketone median level and urine ketone median level in emesis and hyperemesis gravidarum was 0.1, 95% CI (0.03–0.20), 0.7, 95% CI: 0.30–1.00, p<0.0001, and 0, 95% CI: 0.00–0.00, 2, 95% CI: 1.00–3.00, p<0.0001, respectively.

Conclusion: A rapid, bedside capillary blood ketone measurement can reliably help to diagnose hyperemesis gravidarum in patients with pregnancy-induced nausea and vomiting.

Keywords: Ketone body, hyperemesis gravidarum, emergency

Introduction

Pregnancy-induced nausea and vomiting (PINV) is a common problem at the early stages of pregnancy. Approximately, 50%–80% of pregnant women who are in their first trimester are affected, resulting in loss of work time and negative effects on social and family relationships (1). Hyperemesis gravidarum (HG) affects approximately 2.5% of pregnant woman and is characterized by persistent vomiting, weight loss of more than 5%, dehydration, ketonuria, electrolyte abnormalities, acid–base imbalance, and sometimes hepatic and renal failure (2).

Currently, there is no consensus on the definition of HG and there is no single, widely used set of diagnostic criteria for diagnosing HG at the emergency department (ED). There are commonly used diagnostic modalities with low sensitivity, such as clinical findings of patients, weight loss, dehydration, and/or electrolyte imbalance, and ketonuria (3). Urine ketone dipstick tests are used in the ED to screen for ketonuria in patients with PINV to detect metabolic derangements in the early phases. Although urine ketone dipsticks tests routinely measure urinary acetoacetate, they do not detect the ketone predominant in HG, which is β-hydoxybutyric acid (β-HBA). In the

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literature, studies mainly focus on determining acetoacetate levels, which is a urine ketone (4-6). Since acetoacetate is a metabolite of β-HBA, and the determination of acetoacetate levels in urine is time consuming, using point-of-care capillary blood levels of β-HBA may result in early diagnosis and treatment before ketonuria becomes apparent (7). To date, capillary β-HBA testing has not been used to diagnose HG in PINV at the ED. The aim of this study was to determine the accuracy of point-of-care blood ketone tests in diagnosing HG in patients who are admitted to the ED with PINV.

Materials and Methods

This study used a retrospective cohort for a single-center clinical trial of pregnant patients aged >18 years who were admitted to the ED with nausea and vomiting between January 1, 2008 and December 31, 2012, at a tertiary medical center with 90,000 patients per year. Before the study start, the Akdeniz University Clinical Research Ethics Committee approved all permits.

Pregnant women of <16 weeks of gestational age were included. Patients admitted with nausea and vomiting as the principal complaint were tested for capillary blood ketone and urine ketone. Patients with other systemic diseases that could cause nausea and vomiting and those without files were excluded from the study.

The diagnosis of HG was based on the following criteria: (1) persistent nausea and vomiting requiring hospitalization in ED and (2) weight loss of more than 5% with nausea and vomiting.

Data recorded included complaints, age, obstetric history, date of last menstrual period, vital signs (blood pressure, arterial pulse, fever, respiratory rate, and oxygen saturation), capillary blood, urine ketone values upon admission, and length of hospital stay. Pregnancy-unique quantification of emesis and nausea (PUQE) scores were calculated according to the complaints of patients upon admission and were classified as mild, moderate, or severe.

Capillary blood ketone was measured at the bedside and the results were noted in patients' file. The test was conducted using 0.1 mL of blood dropped into the blood compartment of the Medisense Optimum β-Ketone Test Strip® (Abbott Diabetes Care Ltd., Witney, Oxon, UK) to measure capillary blood ketone. Subsequently, data obtained from an OptiumXceed® blood ketone meter (Abbott Diabetes Care Ltd. Witney, Oxon, UK) were recorded in patients' files. Tests results were positive if capillary β-HBA was ≥0.1 mg/dL. Urine ketone values were classified as negative (0), positive one (+1), positive two (+2), positive three (+3), or positive four (+4).

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) 16.0 and Medcalc 11.0.4. Continuous variables are expressed as mean ± standard deviation (SD). Variables that did not meet the normal distribution were expressed as medians (interquartile ratio [IQR]) and frequency variables were expressed as percentages. The diagnostic capabilities of the parameters used in this study were tested with sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR). Variables were evaluated and recorded. Student's t-tests and chi-square tests were used to determine statistically significant results and differences between the groups at a $p<0.05$ level of significance.

Table 1. Diagnostic accuracy of blood ketone and urine ketone levels

	Emesis gravidarum (n=70)	Hyperemesis gravidarum (n=32)	p
Capillary blood ketone, median (95% CI)	0.1 (0.03–0.20)	0.7 (0.30–1.00)	<0.0001
Urine ketone, median (95% CI)	0 (0.00–0.00)	2 (1.00–3.00)	<0.0001

Table 2. Relationship between capillary blood ketone and urine ketone

	0, (63)	1+, (11)	2+, (11)	3+, (9)	4+, (8)
Capillary blood, ketone median (IQR)	0. (0.00-0.20)	0.2 (0.20-0.37)	0.5 (0.20-0.37)	1 (0.55-1.45)	1.3 (0.95-3.20)

Table 3. Diagnostic accuracy of HG with the capillary blood ketone levels

Capillary blood ketone	Sensitivity, % (95% CI)	Specificity, % (95% CI)	+LR (95% CI)	-LR (95% CI)
>0	96.8 (83.8–99.9)	38.5 (27.2–51.0)	1.58 (1.5–1.9)	0.081 (0.01–0.6)
>0.6	53,1 (34.7–70.9)	94.3 (86.0–98.4)	9.3 (3.4–25.4)	0.5 (0.3–0.7)
>0.8	40.6 (23.7–59.4)	98.5 (92.3–100)	28.4 (3.9–208.1)	0.6 (0.5–0.8)

Table 4. Relationship between fingertip blood ketone with PUQE subgroups

	PUQE score (n)			
	1, (6)	2, (73)	3, (23)	p
Capillary blood ketone, median (IQR)	0.0 (0.0–0.1)	0.1 (0.0–0.32)	0.8 (0.20–1)	0.000212

Results

During the study period, a total of 177 pregnant women with nausea and vomiting were admitted to the ED. Seventy-three of these patients' files could not be found in the archives. Two patients were excluded because they did not meet the inclusion criteria. Statistical analyses were performed using 102 patients' data.

The mean age of the 102 patients was 27.6±5.1 years; the average duration of pregnancy was 63.1±2 days. Seventy patients (68.6%) were diagnosed with emesis gravidarum (EG), and 32 hospitalized patients (31.4%) were diagnosed with HG. The mean level of the capillary blood ketone and the median level of the urine ketone upon admission were 0.45±0.85 and +2, respectively. Both capillary blood ketone and urine ketone levels were found to be statistically significant for the diagnosis of HG in patients with PINV. The diagnos-

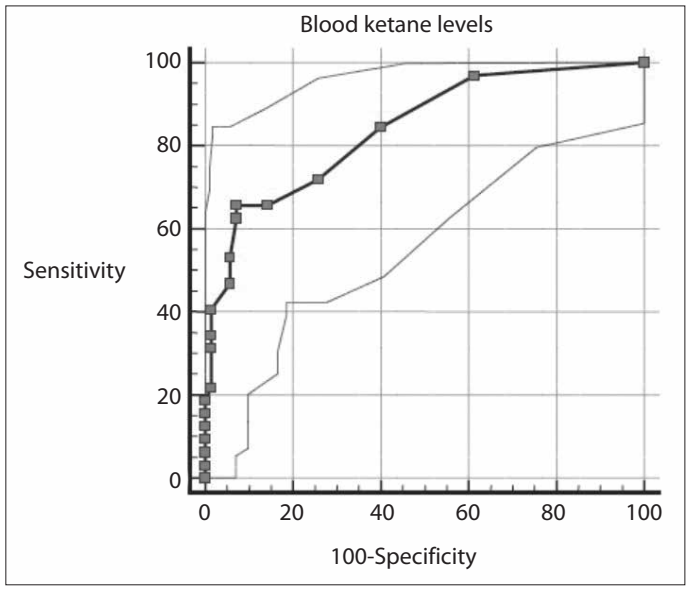

Figure 1. The relationship between capillary blood ketone and urine ketone levels

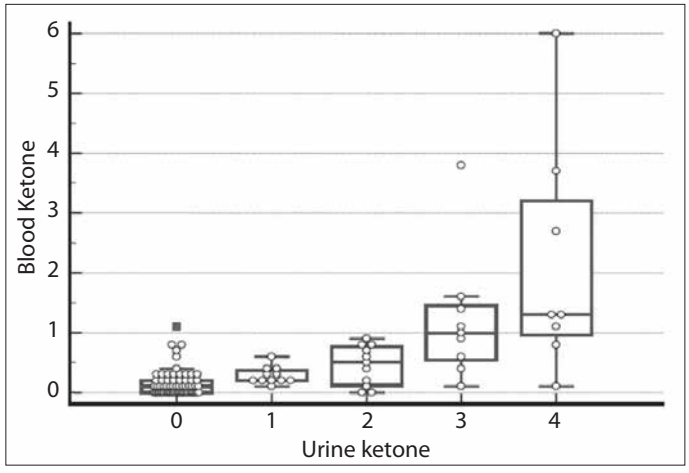

Figure 2. Diagnostic accuracy of HG with the capillary blood ketone levels

tic accuracy of the capillary blood ketone and urine ketone measurement for HG is shown in Table 1. A post-hoc analysis showed that the values of urine ketone and capillary blood ketone were significantly correlated. This relationship was more pronounced in patients with low urine ketone values. The relationship between capillary blood ketone and urine ketone is clearly shown in Table 2 and Figure 1.

Area under the curve (AUC) and receiver operating characteristic (ROC) analyses were performed. At the 95% confidence interval (CI) for diagnostic accuracy, capillary blood ketone levels can diagnose HG at 0.841 (95 % CI: 0.755–0.906, p<0.001). Statistical data for the diagnostic accuracy of capillary blood ketone levels in the diagnosis of HG are shown in Table 3, and the ROC curve is shown in Figure 2.

The median values (95% CIs) of PUQE for the EG and HG were 10 (9–11) and 12 (11–13), respectively, and the relationship was found to be statistically significant (p<0.0001).

Upon examination of a subcategory of PUQE, fingertip blood ketone levels in patients with PINV were statistically significant; statistical data are presented in Table 4.

Discussion

As seen in this study, 177 pregnant patients admitted to the ED with various medical complaints were part of the 5-year study. Emergency physicians need to identify mortal and morbid complications of pregnancy accurately and rapidly. EG and HG are among the most well-known complications, and in the first 16 weeks, they are known as PINV syndromes. It is extremely important to be able to distinguish these two clinical cases in the ED. A patient with EG can be discharged after appropriate liquid and antiemetic therapy in the ED, while a patient with HG and dehydration, weight loss, and electrolyte imbalances may need to be hospitalized (7). However, there are no clear and concise diagnostic criteria for HG in the ED. The most commonly used diagnostic markers are prolonged and persistent nausea and vomiting, weight loss with electrolyte abnormalities, ketonuria, and dehydration (3). Previous studies have shown that urine ketone levels are widely used as a laboratory test for diagnosing HG in patients with PINV. These studies revealed that urine ketone levels of patients with HG were increased (3+ [50 mg/mL] or 4+ [100 mg/mL]); however, no clear information was provided regarding the diagnostic accuracy of ketone levels for HG in patients with PINV (4-6). Our study was a comparison of the capillary blood and urine ketone levels of 32 patients diagnosed with HG and 70 patients diagnosed with EG after being admitted to the ED with PINV. As evident from the results, the median value (95% CI) of capillary blood ketone was 0.7 mmol/L (0.30-1.00) and found to be statistically significant (p<0.0001). Alternatively, the diagnostic accuracy of capillary blood ketone for diagnosing HG in patients admitted to the ED with nausea and vomiting who have a capillary blood ketone level >0.8 mmol/L was found to be 28.4 (3.9-208,1) with +LR and 0.6 (0.5-0.8) with -LR; AUC (95% CI) was found to be 0.841 (0.755-0.906, p<0.001). There is a strong correlation between the measured values and urine ketone levels, particularly at low levels. There are no studies in the literature equivalent to this study because it is the first clinical trial with capillary blood ketone measurements. The values show a positive correlation with the results of the capillary ketone measurement's prospectus. In the prospectus of the test, normal ketone level was 0.1-8.0 mmol/L. β-HBA levels were classified as low (0.4-0.8 mmol/L), moderate (1.8-2.8 mmol/L), or high (>3.2 mmol/L) (8). Acetest and Ketostix (Ames Co.) are semiquantitative tests that are widely used to measure acetoacetate and acetone. Acetoacetate and acetone are a small part of the serum and urine ketones. The main ketone in the serum is β-HBA. These tests are not sensitive to β-HBA and are only useful in predicting total ketone bodies. Acetoacetate and acetone are formed after β-HBA metabolism and eliminated in the urine. Thus, urine ketone bodies are formed in small amounts or cannot be determined at the early stage of HG (8). As a result of this study, fingertip blood ketone >0.8 mmol/L can be used for an early diagnosis and treatment for HG, contributing to reducing the rate of maternal complications. PUQE was the scoring system for PINV severity with three classifications: low (≤6), moderate (≤7≤12), and high (≤13) (9). In our study, the median PUQE of 10 (IQR, 9-11) and 12 (IQR, 11-13) were used to diagnose EG and HG, respectively; these scores were found to be statistically significant at p<0.0001. Emesis or hyperemesis can only be diagnosed using PUQE scores. In addition, the median for capillary blood ketone levels of preg-

nant patients with severe nausea and vomiting (PUQE ≥13) was 0.8 (IQR, 0.2-1.1). For patients admitted to the ED with PINV and capillary blood ketone levels of ≥0.8, the diagnosis of HG had a sensitivity of 40% and specificity of 98.5%. Considering that this is the first clinical study to measure capillary blood ketone, currently, there are no studies in the literature that can evaluate the results of PUQE scores with capillary blood ketone levels.

Study limitations

The most important limitation of this study is that is a retrospective study. All of the study data were obtained from the hospital database. Pregnant patients who were not tested for blood or urine ketone levels were not included and that may affect our results.

Another limitation is the inadequate criteria in diagnosing EG and HG. A literature review revealed different diagnostic criteria and applications of these criteria among different clinics.

When the study was initiated, the diagnosis of HG was defined as admission to the ED after persistent nausea and vomiting with weight loss of more than 5%.

Another limitation is that reference venous blood β-HBA was not measured in the laboratory. Formal laboratory testing of venous blood β-HBA is time consuming and not practical and therefore is not routine for busy ED clinics. Recently, ketone sensors have been offered to diabetic patients to measure electrochemical β-HBA in blood. The determination β-HBA within 5 seconds with 10 µL of capillary blood sample has been reported. A few comparisons have been performed under laboratory conditions with volunteers and random blood samples. Hilary et al. (10) reported a strong correlation between the capillary-blood and laboratory-measured serum β-HBA.

Conclusion

A rapid, bedside capillary blood ketone measurement can reliably help to diagnose hyperemesis gravidarum in patients with pregnancy-induced nausea and vomiting. There is a strong correlation between capillary blood ketone and urine ketone values, particularly at low levels. Therefore, in these patients, capillary blood ketone measurement can be used instead of urine ketone measurement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Akdeniz University School of Medicine.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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