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Original research

Comparison of bicarbonate values from venous blood gas and chemistry panels measured at the time of diagnosis and resolution of diabetes ketoacidosis

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A B S T R A C T

Objective: To determine if bicarbonate values from venous blood gas (VBG) and plasma chemistry samples provided agreement in determining the bicarbonate criteria for the diagnosis and/or resolution of diabetic ketoacidosis (DKA).
Methods: A retrospective chart review of data from patients admitted to a tertiary care hospital with a diagnosis of DKA over a four year period was performed. Paired bicarbonate values from a VBG and chemistry panel, if drawn within 60 minutes of each other, were compared.
Results: At the time of diagnosis of DKA, 197 paired bicarbonate values were available for analysis with the mean difference between the two methods of testing of 2.5 mmol/L. 16 of the 197 (8%) paired values were discordant in meeting criteria for diagnosis of DKA. At the time of resolution of DKA, 83 paired bicarbonate samples were compared. The mean difference was 2.3 mmol/L. 20 of the 83 (24%) paired bicarbonate values showed discordance with regards to meeting the bicarbonate criteria for resolution of DKA.
Conclusion: Discordance between bicarbonate results from different analysis methods may lead to different determinations as to whether or not a patient meets the biochemical definition for diagnosis and resolution of DKA.

Diabetic ketoacidosis (DKA) is a severe acute complication of uncontrolled diabetes. This diabetic emergency is diagnosed by the following criteria: blood glucose > 250 mg/dl, the presence of ketonemia and the presence of acidosis (arterial pH ≤ 7.30 and bicarbonate ≤ 18 mmol/L) [1]. Treatment includes correcting fluid and electrolyte abnormalities and administering insulin to correct the acidosis and lower blood glucose levels. The use of an insulin infusion, especially in the setting of severe DKA, is considered the standard of care. Patients with DKA are monitored more frequently with clinical and laboratory evaluation than patients with hyperglycemia and no other metabolic abnormalities. In order to determine when DKA has resolved, once blood sugars are less than 200 mg/dl, two of the following three criteria should be met: pH > 7.30, normalization of the anion gap and increase of the bicarbonate level to ≥ 15 mmol/L [1].

Traditionally, a chemistry panel has been used to determine electrolyte levels including bicarbonate levels. In practice however, clinicians may use bicarbonate levels obtained from a venous chemistry panel or via arterial or venous blood gas analysis. The advantages of using a venous blood gas (VBG) include the avoidance of potential trauma and pain associated with an arterial blood gas draw, which can be technically difficult, and a more rapid processing time compared to a venous chemistry sample. However, venous chemistry samples provide other relevant information such as creatinine, and the benefit of a measured serum bicarbonate level whereas bicarbonate results from a VBG are calculated via the Henderson-Hasselbalch equation based on direct measurement of pH and PCO_2. The causes and extent of the discordance between measured and calculated bicarbonate values has been discussed in other work. Some studies have found differences between measured and calculated bicarbonate to be clinically insignificant [2–4], though others have not [5,6].

There have been several studies comparing bicarbonate values from arterial blood gas (ABG) to VBG samples in DKA, but not many comparing the use of values from a VBG vs a chemistry panel [7–11]. There have been no studies evaluating the implications of using VBG bicarbonate levels to evaluate DKA resolution. The purpose of our study was to compare the results of VBG and plasma chemistry bicarbonate

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levels obtained in the setting of routine medical care at the time of both the diagnosis and resolution of DKA to determine whether the results would show concordance as to the biochemical status of the patient.

Methods

Study Design: The study, which was approved by the Boston University Medical Center Institutional Review Board, is a retrospective chart review of data from patients admitted to the institution over a four year period between 2011 and 2014. The initial data was extracted from the electronic medical record (EMR) using ICD-9 diagnostic codes for DKA (250.12 and 250.13) and investigators subsequently reviewed each chart to confirm eligibility. Patients were included in the study if they were 18 years of age or older at the time of admission, were admitted to the hospital with a diagnosis of DKA and had a bicarbonate value from a VBG and chemistry panel within 60 min of each other at the time of diagnosis and/or at the time of resolution of DKA. For the diagnosis of DKA, the criteria of blood glucose $>$ 250 mg/dl, presence of ketones in urine or blood, serum pH $\leq$ 7.30 and bicarbonate $\leq$ 18 mmol/L (on a VBG or chemistry panel) was used. In cases where urine and blood ketones were not checked, if the history and presentation was consistent with a probable diagnosis of DKA, the data was included for analysis. To determine resolution by bicarbonate criteria, the first bicarbonate value $\geq$ 15 mmol/L, either on a VBG or chemistry panel, was selected. If the chemistry panel was the first to show diagnosis of DKA or resolution by bicarbonate criteria, a paired value from the VBG panel within 60 min was documented and vice versa. If no paired bicarbonate value was available, the data was not included for analysis. The bicarbonate level on the chemistry panel was determined by using Architect c8000 (Abbott Diagnostics, Abbott Park, IL) via a PEP carboxylase reaction and venous blood gas analysis was performed using Radiometer ABL800 FLEX analyzer (Radiometer, Brea, CA). Bicarbonate values from VBG samples are calculated using the Henderson-Hasselbalch (HH) equation: $pH = pK_a + \log_{10}([HCO_3^-]/[H_2CO_3])$. All of the measurements were performed in the chemistry laboratory at the Boston Medical Center as part of the patients' routine clinical care.

Data Analysis: General characteristics were analyzed using standard descriptive statistics. Paired bicarbonate values from VBG and chemistry panels at the time of diagnosis or resolution of DKA were compared if drawn within 60 min and 30 min of each other. Student's *t* test was used for comparison. If the bicarbonate value was resulted as $<$ 5 mmol/L on the chemistry panel or VBG, a value of 5 mmol/L was used for analysis.

Results

Data from 313 admissions were obtained from the EMR based on age and diagnostic code criteria. After reviewing each admission, 95 were excluded for not meeting criteria for DKA, 13 did not have paired bicarbonate values at the time of diagnosis and/or resolution of DKA and three were not unique inpatient admissions. 202 admissions were included for the final analysis. Table 1 outlines the basic demographic characteristics and admission laboratory values for the study cohort.

At the time of diagnosis of DKA, 197 paired bicarbonate values were available for analysis that were drawn within 60 min of each other, 191 samples that were drawn within 30 min of each other and 165 of these were drawn simultaneously. The mean bicarbonate level from the VBG and chemistry panels were 11.38 ± 4.51 and 9.01 ± 3.48 respectively. The mean difference between the paired samples was 2.5 ± 1.7 mmol/L (range 0–9.4 mmol/L) and was statistically significant ($p < 0.01$). With regards to the clinical significance of these differences, 16 of the 197 paired values were discordant in meeting the bicarbonate level criteria for the diagnosis of DKA. In all 16 cases, the bicarbonate value from the VBG sample was $>$ 18 mmol/L and would exclude a diagnosis of DKA.

Table 1
Demographics and baseline laboratory profile of the study cohort at the time of admission and diagnosis of DKA.

Demographic Data	
Age (years) [mean ± SD (range)]	41.49 ± 15.74 (18–88)
Gender	
- Male [%]	121 (59.9%)
- Female [%]	81 (40.1%)
Baseline Laboratory Data	
Glucose (mg/dL) [mean ± SD (range)]	633.83 ± 272.33 (251–1971)
Bicarbonate level (mmol/L), [mean ± SD (range)]	8.96 ± 3.41 (5–18)
pH [mean ± SD]	7.17 ± 0.1
Anion gap [mean ± SD]	25.74 ± 5.67

While being treated for DKA, 83 admissions had paired bicarbonate samples (with at least one value $\geq$ 15 mmol/L) within 60 min of each other and 75 within 30 min of each other. 49 of the paired samples were drawn simultaneously. The mean bicarbonate level from the VBG and chemistry panels were 18.2 ± 2.37 mmol/L and 16.11 ± 2.27 mmol/L respectively. Similar to the labs drawn at the time of diagnosis of DKA, there was a statistically significant difference between bicarbonate values from the VBG and the chemistry panel ($p < 0.01$). The mean difference was 2.3 ± 1.3 mmol/L (range 0–5.8 mmol/L). 20 of the 83 paired bicarbonate values showed discordance with regards to meeting the bicarbonate level criteria for resolution of DKA. Eighteen of these samples did not meet the criteria based on the bicarbonate value from the chemistry panel and the remaining two did not meet criteria based on the VBG bicarbonate level.

Discussion

In the acute setting, identification of DKA and its severity helps in the triage of patients to an appropriate level of care. Furthermore, providers may choose to manage patients differently if the patient meets a biochemical diagnosis of DKA, such as using higher insulin doses or an insulin infusion, or to determine if the patient is felt to be stable to discharge back to the community. An admission for the diagnosis of DKA may influence the treatment that is recommended for the patient upon discharge from the hospital. Similarly, providers await the improvement of bicarbonate as a marker that the patient is stable for transition off an insulin infusion. While the absolute difference between some of the paired bicarbonate levels was not great, the use of threshold cutoff values to determine resolution means that even a slightly lower value may cause the provider to delay transition to subcutaneous insulin therapy, or potentially transition prematurely. While prior recommendations for a bicarbonate cutoff to determine the resolution of DKA was $\geq$18 mEq/L, more recently the recommended cut-off is $\geq$ 15 mEq/L [1,12]. It is not known if one cut-off is clinically superior in terms of patient outcomes, or if small differences in bicarbonate levels at the time of transition to subcutaneous insulin have an impact on outcomes.

As mentioned previously, several studies have looked at the correlation between measured and calculated bicarbonate levels and determined in most situations the absolute differences are not large and therefore not clinically significant. In one study, Kobold et al. compared measured venous bicarbonate and calculated arterial bicarbonate results drawn concurrently on 17,621 samples. This group found the mean difference to be 0.36 mmol/L, and agreement of values within 3 mmol/L in 98.5% of samples [13]. Another study of 1820 simultaneously drawn ABG and venous chemistry samples showed overall good correlation, however significant discrepancies between certain calculated and measured values, in particular when bicarbonate values were lower [14]. There is limited data comparing different bicarbonate

measurement methods in patients with DKA. In a prospective observational analysis of data from patients admitted to the emergency department, Menchine et al. compared the accuracy of VBG electrolytes including bicarbonate levels for diagnosing DKA to plasma chemistry panels for diagnosing DKA [15]. Of 342 patients with paired VBG and serum chemistry panels, 46 were diagnosed with DKA. This study found that the sensitivity and specificity of VBG electrolytes in the diagnosis of DKA were 97.8% and 100% respectively.

There are a number of factors that are known to contribute to differences between measured and calculated bicarbonate values. These include assay interference, loss of CO_2 gas during processing, CO_2 accumulation due to tourniquet induced venous stasis, and variation of pḰ from the assumed value in the HH equation, among others [5,16–18]. One case report determined the wide difference between measured and calculated results in an individual patient to be due to human error when calculating the HCO_3^- from the VBG [19]. While clinicians may in general feel more comfortable relying on the results of a measured value, other studies have demonstrated potential interference from lipemia and paraproteinemia with chemistry panel bicarbonate results, including those that use photospectometric analysis [16,20].

In our study, we found a clear bias toward measured chemistry values being lower than values calculated for VBG results (Fig. 1). The reasons for this difference were not clear. We considered whether time between sample draws might have allowed time for an actual change to have occurred in the patients' bicarbonate value. However, we did not find a correlation when comparing time difference between samples (Fig. 2a, b), or that later values were consistently higher than values obtained earlier in the patients' clinical course. We also considered if sample processing delay could have affected measured bicarbonate results as chemistry samples take longer to transport and process. However, our lab undertook a quality review and measured bicarbonate on serial samples over several hours, and it did not find any significant change in measured values when sample measurement was delayed with time.

Our current study has several strengths. First, all patients were determined to meet criteria for DKA by investigator chart review, and we did not rely on ICD-9 code alone. Furthermore, the same instruments were used during the course of the study to analyze samples. Finally, these samples were all obtained in the course of routine clinical care, and would reflect values that were available to assist providers in the care of patients in real-time. However, there are also some limitations to this work. As this was a retrospective analysis of data, it has the limitation of not controlling for pre-analytic factors that could affect the bicarbonate results. Since beta hydroxybutyrate and urine ketone levels were not available for all patients (24 of 202 patients), there could have been an incorrect diagnosis of DKA and inclusion in the study cohort. Not all paired bicarbonate levels were drawn at the same time, and we

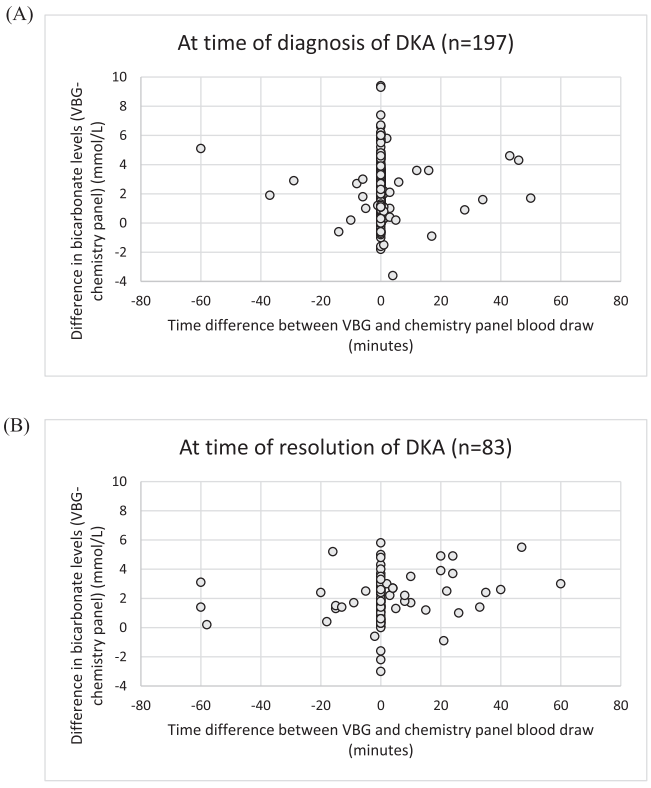

Fig. 2. Differences in bicarbonate values from VBG and chemistry panel for individual patients at (A) the time of diagnosis of DKA and (B) time of resolution of DKA.

cannot completely rule out any effects of a time delay, though as mentioned above we did not see any correlation. A prospective study where paired samples are drawn and analyzed simultaneously could potentially decrease some sources of variation. Additionally, our findings are based on the performance of the particular blood gas and chemistry analyzers used at our institution. Clinical application of this study would need to take into account these factors when applying it to other populations and institutions. Finally, our study does not help us determine the "right" method (measured vs calculated bicarbonate) to use in all clinical situations. It also is not an assessment on whether VBG can replace ABG testing which plays an important role in the diagnosis of DKA. While the tendency of the provider may be to rely on measured values, the limitations of these assays must be understood, and in particular in patients in whom there is a wide discordance between measured and calculated values further investigation should be

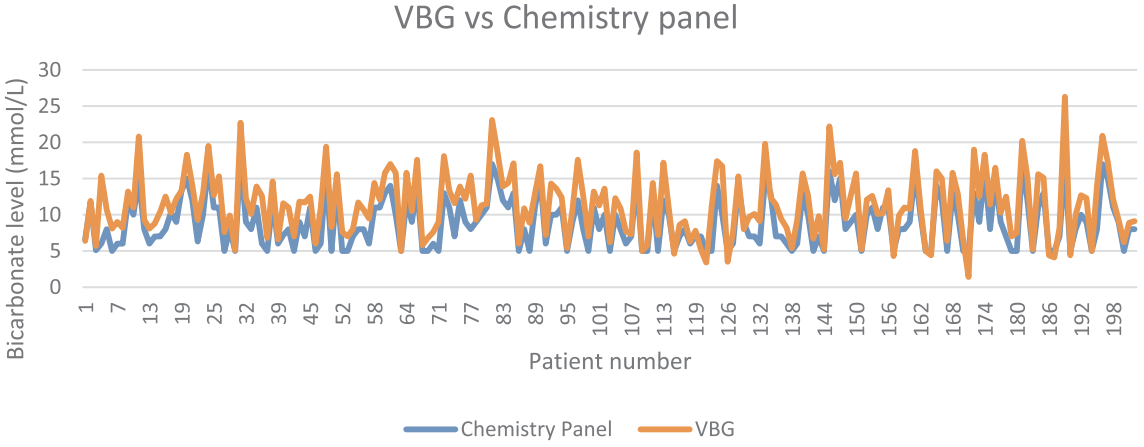

Fig. 1. Comparison of bicarbonate results by different methods.

undertaken.

In conclusion, our study demonstrates discordance in some patients when establishing the criteria for a diagnosis or determining resolution of DKA depending on the method used to assess bicarbonate. Clinicians should consider the limits of laboratory testing when making diagnostic and treatment decisions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2019.100205.

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