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Pyloric Stenosis and Nonbilious Vomiting in Infants: Negative Base Excess and Hypercapnia—Two Opposing Points of One Scale a Comparative Case Series

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Abstract

Background: Blood pH and bicarbonate estimations are basal acid-base laboratory tests that are performed in infants with infantile hypertrophic pyloric stenosis (IHPS). This study aimed to define the clinical value of pCO_2 and BE in infants suspected to have IHPS. **Methods:** We collected data from 80 "surgical" infants younger than 100 days with prolonged nonbilious vomiting who were suspected to have IHPS. In 65 infants, pyloric stenosis was confirmed, and 15 infants had nonsurgical conditions. Capillary blood was tested for standard acid-base parameters and lactate. The two groups were compared. **Results:** Eighty-eight percent of the IHPS infants had elevated standard bicarbonate levels (st bicarb) > 25 mmol/l, and 60% had BE > 3.5 mmol/l; 12% of the infants showed hypercapnia ($pCO_2 \geq 50$ mmHg) associated with markedly increased standard bicarbonate and BE. Infants with nonsurgical vomiting were older at admission ($p = 0.002$), had a longer duration of vomiting ($p < 0.001$), were older ($p = 0.002$) and weighted more at admission ($p = 0.004$), had lower pCO_2 ($p = 0.021$), lower st bicarb ($p < 0.001$) and lower BE ($p = 0.001$). In addition, nonsurgical infants showed a trend to anemia ($p = 0.002$). **Conclusions:** In infants with IHPS/nonbilious vomiting, acid-base analysis (ABA) is equivocal or inconclusive. These findings may be misleading and could result in a false clinical decision. Nonsurgical vomiting is associated with a lower degree of alkalosis, normocapnia to slight hypercapnia and a base deficit. However, even infants with IHPS may present with a negative BE. In infants with IHPS and severe alkalosis, hypercapnia carries a risk for respiratory depression. Monitoring the infant's respi-

ration allows for the early detection of respiratory deterioration.

Keywords

Pyloric Stenosis, Nonbilious Vomiting, Hypoventilation, Base Excess, Hypercapnia

1. Introduction

Nonbilious vomiting (NBV) occurring shortly after feeding is commonly observed in first trimester infants. Infantile hypertrophic pyloric stenosis (IHPS) is the most important surgical condition associated with projectile NBV. It occurs between 3 and 12 weeks of age. The diagnosis of IHPS is confirmed with high efficacy by ultrasound investigation. Acid-base analysis (ABA) adds important information regarding the presence of metabolic alkalosis and dehydration. According to Henderson-Hasselbalch, bicarbonate (HCO_3^-) and carbon dioxide partial pressure (pCO_2) are basic parameters used to characterize the acid-base status. Bicarbonate is considered the gold standard for estimating the degree of alkalemia, and pCO_2 is of major interest regarding the respiratory situation. Only a small minority of existing studies have focused on the role of pCO_2 in nonbilious vomiting. In contrast, base excess (BE) is a derived parameter. Previously, it has been hypothesized that the estimation of BE might be superior to that of bicarbonate [1]. Herein, we present an investigation that focuses on the role of BE in infants with NBV and/or IHPS, and we characterize a new subgroup with negative BE.

2. Methods

Between January 2014 and December 2017, we collected data from 80 infants younger than 100 days admitted to the Department of Pediatric Surgery, Ruhr-University of Bochum, St. Marie's Hospital Witten, with NBV under the suspicion of IHPS. Ultrasound examination and standard ABA were performed for all the patients at admission. Lactate was estimated in 73 of the 80 patients. Each infant received a gastric tube. IHPS was confirmed at surgery in 65 infants (no negative pyloric exploration, one failed diagnosis), and 15 infants had non-surgical diseases (gastroesophageal reflux [GER], 10; infection 5). A blood gas analyzer (GEM Premier 4000®-Device, Instrumentation Laboratory, Lexington, MA, USA) was used to measure pH, pCO_2, sodium, lactate and hematocrit. For this study, we primarily focused on the actual BE, defined as the concentration of titratable base when the whole blood is titrated under standard conditions (pH 7.40; pCO_2 40 mmHg; temperature 37°C). We used the term "base deficit" interchangeably with a negative BE. The degree of dehydration was calculated as the difference between the final weight at discharge and the initial weight divided by the final weight × 100. For the interquartile range (IQR), we used the 1st and 3rd quartiles.

The Kolmogorov-Smirnov normality test was used show normal distribution

(Table 1). We used the two-sample Student's t test and the nonparametric Mann-Whitney test. Region-under the-curve analysis (ROC) was performed to evaluate the optimal cutoff for the predictive value for IHPS (Youden index, *J*).

The study was performed in accordance with the Declaration of Helsinki. Institutional review board approval was obtained from the Ethics Committee of the Ruhr-University of Bochum [Register No. 16-5604].

3. Results

Biometry (Table 1): The infants with IHPS were younger at admission (median, 35 vs. 67 days, p = 0.002) and had a lower body weight (median, 3.3 vs. 4.5 kg, p = 0.004). The median duration of enhanced vomiting was 1 day for the IHPS infants and 4 days for the nonsurgical group. The degree of dehydration was predominantly slight to moderate (median, 3.3 vs. 2.0%, p = 0.650). In the infants with IHPS, the median preoperative stay on the ward was 1.5 days, and the total length of stay was 5 days. The weight gain of the infants was not different between the groups.

A graphical overview of the patient stratification and the main results of ABA are provided in Figure 1.

Ultrasound morphometry: We had one delayed diagnosis of IHPS due to a misinterpretation of a primarily enlarged pylorus. Generally, there was a significant difference regarding ultrasound pyloric muscle length (19.9 ± 3 vs. 15.3 ± 4 mm; p < 0.001) and muscle thickness (6.1 ± 6.8 vs. 3.9 ± 1.7; p = 0.003). Pyloric muscle thickness above the cutoff value of 4.9 mm had a positive likelihood ratio

Table 1. Biometry and laboratory results (median value; 1st - 3rd quartile).

Parameter	IHPS Median (IQR)	Nonsurgical Median (IQR)	p value
Duration of symptoms	1 (1 - 2)	4 (1 - 17)	<0.001
Age at admission [d]	35 (28 - 48)	67 (44 - 97)	0.002
Weight [g]	3300 (3440 - 4225)	4495 (3990 - 4813)	0.004
Gain of weight [g]	118 (23 - 241)	90 (50 - 188)	0.920
Degree of dehydration [% of weight]	3.3 (0.8 - 5.8)	2 (1.2 - 3.7)	0.650
Blood pH	7.45 (7.42 - 7.5)	7.44 (7.41 - 7.47)	0.155
pCO_2 [mmHg]	42 (38 - 46)	38.5 (31.3 - 40.8)	0.021
St bicarbonate [mmol/l]	28.6 (26.3 - 31.3)	25 (23.9 - 25.7)	<0.001
Base excess [mmol/l]	5.0 (2.4 - 8.3)	0.6 (−1 - 2.5)	0.001
Sodium [mmol/l]	135 (135 - 138)	138 (136-138)	0.251
Lactate [mmol/l]	1.8 (1. - 2.2)	2.1 (1.5 - 2.7)	0.174
Hemoglobin [g/dL]	13.4 (11.9 - 15.3)	11.1 (10.4 - 12.4)	0.002
Hematocrit [%]	37 (32 - 43)	31 (29.5 - 35.5)	0.056

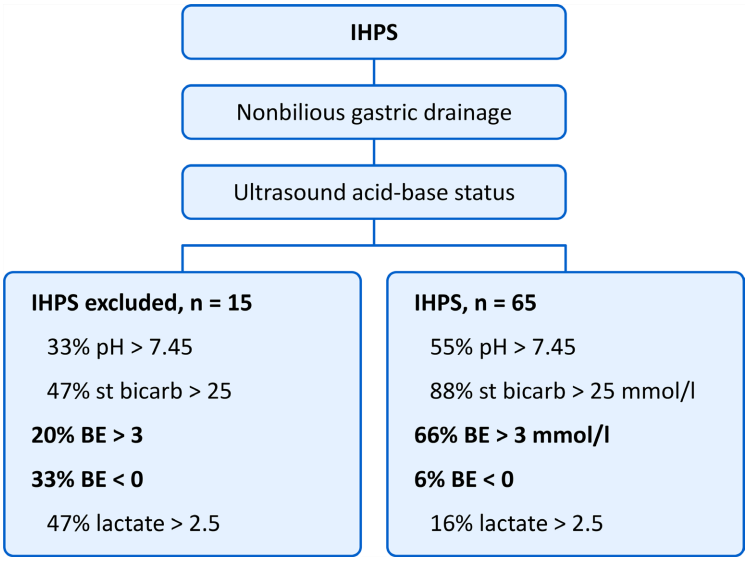

Figure 1. Flow chart of the investigation and main results of the investigation. Infants with IHPS versus nonsurgical disease.

of 6.5; pyloric length >15.5 mm had a likelihood ratio of 2.4.

Acid-base and blood gas analysis (Figures 2(a)-(e)): ABA revealed alkalosis with pH ≥ 7.45 in 55% (n =36) of the IHPS patients and in one patient (7%) among the nonsurgical infants. The blood pH was similar in both groups (median, 7.45 vs. 7.44, p = 0.155). Standard bicarbonate (st bicarb) was higher in the IHPS group (median, 28.6 vs. 25 mmol/l, p < 0.001). Standard bicarbonate values > 25 mmol/l were found in 88% (n = 57) of the patients with IHPS and in 47% (n = 7) of the patients without surgery. Highly elevated standard bicarbonate ≥ 28 mmol/l was found in 54% (n = 35) of the patients with IHPS and in 47% (n = 7) of the patients without surgery.

pCO_2 was higher in the IHPS group (median, 42 vs. 38.5 mmHg, p = 0.021). Hypercapnia with pCO_2 > 50 mmHg was seen in 12% (n = 8) of the infants with IHPS and in 14% of the nonsurgical infants.

Hemoglobin was significantly higher in the IHPS patients (median, 13.4 vs. 11.1 g/dL, p = 0.002). Slight anemia (Hb < 10 g/dL) occurred only in 4 infants with IHPS (6%) and in 2 infants in the nonsurgical case group (13%). No patient received erythrocyte transfusion.

There was no significant difference regarding lactate (median, 1.8 vs. 2.2 mmol/l, p = 0.174) or sodium (median, 136.5 vs. 138 mmol/l, p = 0.251). In the thirteen patients with elevated lactate, BE ranged between –6.2 and 9.7 mmol/l. Lactatemia > 2.5 mmol/l was found in 16% (n = 9) of the IHPS patients and in 47% (n =15) of the nonsurgical patients.

Elevated BE > 3.5 mmol/l was found in 60% of the IHPS patients (n = 39) and in only 20% of the controls (n = 3) (median, 5 vs. 0.6 mmol/l, p = 0.001).

A negative BE occurred in 6% (n = 4) of the infants with IHPS (Table 2) and in one-third of the infants (33%, n = 5) in the nonsurgical group. On ultrasound morphometry, all infants with negative BE and IHPS had an increased pylorus

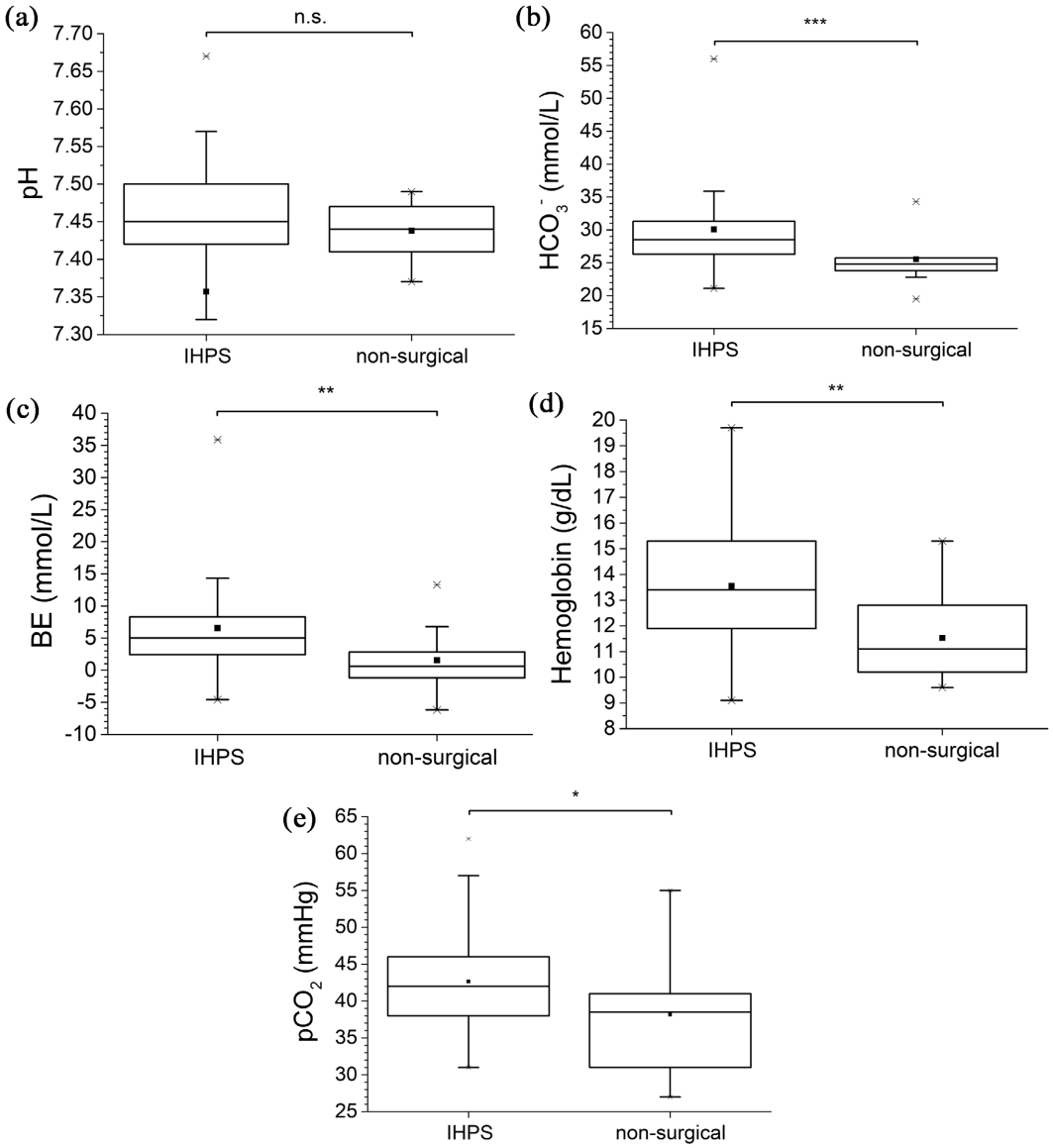

Figure 2. Biochemical results IHPS vs. the nonoperative group (box and whisker plots, median value and arithmetic mean ▪). Statistical significance at p values < 0.05*, < 0.01**, < 0,001***. (a) pH values (not significant); (b) Standard bicarbonate (p < 0.001); (c) Base excess (p = 0.001); (d) Hemoglobin concentration (p = 0.002); (e) Carbon dioxide (p = 0.021).

(median muscle length 20 mm; thickness 4.5 mm), indicating the presence of IHPS.

4. Discussion

The present investigation focused on two cohorts with suspected IHPS. Both groups were defined by age and the leading symptom of repeated nonbilious vomiting.

Generally, repeated vomiting of gastric juice leads primarily to dehydration, and depletion of hydrogen (protons) and chloride ions occurs. The uniform pathophysiology of IHPS may culminate in alkalemia with alkalosis (pH > 7.45,

Table 2. Laboratory results of infants with negative BE and confirmed IHPS (median value). The median values and the interquartile range (IQR) are described in infants with IHPS.

	Case 1	Case 2	Case 3	Case 4	Median (n = 4)	Assessment
Age [days]	41	48	58	52	50	>3rd quartile
Weight [kg]	4.1	3.9	2.3	4.9	4,0	>3rd quartile
Dehydration [%]	7.3	7.2	4.5	0	5.9	>3rd quartile
pH	7.41	7.35	7.41	7.32	7.38	<1st quartile
pCO_2 [mmHg]	38	38	39	37	38	=1st quartile
St bicarb [mmol/l]	24.1	21.1	24.2	24.1	24.1	<1st quartile
BE [mmol/l]	−0.4	−4.6	−0.3	−0.5	−0.5	<<1st quartile
Sodium [mmol/l]	136	142	137	142	139.5	>3rd quartile
Lactate [mmol/l]	3	5.2	1	2.4	2.7	> 3rd quartile
Hb [g/dl]	13.5	11.4	12.6	11.6	12.7	Within IQR
Hct [%]	38	32	32	34	33	Within IQR

elevated bicarbonate) and hypochloremia [2] [3]. If the infant enters an alkalotic state, compensatory mechanisms via the kidneys and lung occur. The kidneys start to excrete bicarbonate and retain hydrogen ions. In addition, potassium is lost in the urine in exchange for hydrogen in an effort to maintain a normal blood pH. If the elevated bicarbonate load is presented to the kidney, the excess bicarbonate may overwhelm the resorptive capacity and accumulate in the blood. As a response to the loss of protons, alkalosis and increasing pCO_2 reflect hypoventilation due to chemoreceptor-initiated inhibition of the brain respiratory center (cyclic breath and hypoxia), which may threaten the infant's life [4] [5].

Thus, ABA and blood gas analysis at admission are acknowledged as important factors within the preoperative evaluation. However, these parameters are not diagnostic for IHPS. Ultrasound, standard bicarbonate and BE were the most important diagnostic parameters in our study. Both groups, IHPS and nonsurgical infants, showed no differences regarding gain of weight during hospital stay, the degree of dehydration, blood pH, sodium, and lactate. However, we found lower standard bicarbonate in the nonsurgical group, which was probably caused by enteral losses due to gastroenteritis.

In infants with IHPS, the degree of alkalosis progressively increases during the period of repeated vomiting [6]. Recently, it was shown in a high-volume monocenter study that easy accessibility to ultrasound did not lead to a lower rate of alkalosis at presentation [7].

More than half of our IHPS patients had a moderate to severe elevation of ≥28 mmol/l. This indicates that there was a higher percentage of patients with alkalemia, as reported previously in a meta-analysis [3]. Despite a longer duration of

vomiting, the patients in the nonsurgical group had lower levels of alkalosis and bicarbonate, and the BE values were lower and often negative (lactate not significantly elevated). In addition, the infants in the nonsurgical group had a trend toward low Hb. This finding can be explained by a longer duration of symptoms and anemia associated with GER or infection, respectively.

The reported different acid-base patterns in the two groups are concordant with previously presented results [2] [8].

However, as we have shown, there exists a very interesting, small group of patients with IHPS who present with base deficits and acidemia (negative BE) (**Table 2**). To the best of our knowledge, negative BE in IHPS patients has not been previously described in detail by other researchers [2] [3] [8]. Exclusively, Mullassery *et al.* [9] reported 2 infants with positive ultrasound, negative BE, and subsequent negative explorations for IHPS. Base deficits in infants with IHPS were previously reported in a small pilot series from our institution [10]. The presented series of a different group of patients confirms our previous observation in a separate group of infants. In clinical practice, negative BE values and lowering of bicarbonate due to dehydration are typical for infants with nonsurgical vomiting due to gastroenteritis or infection [11]. However, in concordance with our pilot series, negative BE occurs in approximately 9% of infants with IHPS. This subgroup was characterized by lower pH, lower pCO_2, lower standard bicarbonate, and higher lactate than the vast majority of infants with IHPS. Hemoglobin and hematocrit were of normal. Increased lactate, as a result of tissue hypoperfusion and acidic ketone bodies, can partly compensate for metabolic alkalosis.

Reduction of hydrogen ions in the blood leads to depression of the infant's ventilation. An increase in arterial blood pH is associated with depression of respiratory centers, resulting in alveolar hypoventilation. In our previous study, we found a strong positive correlation between standard bicarbonate and pCO_2 [10]. In the vast majority of reports from the literature, hypoxemia and hypercapnia have not been reported to be major clinical problems in infants with IHPS. Generally, Feng *et al.* [6] described a significant elevation of pCO_2 in 5% of infants presenting 10 days after the first onset of symptoms (cutoff value at 45 mm Hg, 6 kPa). We used a higher cutoff value of 50 mm Hg (6.66 kPa) and found an elevation of 12% in IHPS infants. None of these infants needed artificial ventilation. It remains controversial whether hypercapnia can lead to respiratory failure. There are at least two case reports regarding preoperatively apneic infants with pyloric stenosis [4] [12]. However, the detailed trigger and incidence of pre- or postoperative apnea in pyloric stenosis are not well known [13].

For clinical practice, we recommend the estimation of pCO_2 and pulse oximetry monitoring of each child with IHPS at presentation.

There are some limitations of this study. All biochemical data were derived from routine blood samples. However, blood from the capillaries is not the same as arterial blood. Increased tourniquet time and prolonged storage and transportation of samples might have contributed to increased pCO_2 and lactate le-

vels. We used a quality-controlled commercial blood gas analyzer. It has been shown that different blood gas analyzers provide good reproducibility and correlation for standard bicarbonate, whereas the estimation of BE depends on the algorithm of estimation and type of analyzer [14] [15]. Finally, but not least in importance, we did not consider the powerful role of chloride anions.

5. Conclusions

In conclusion, despite the broad use of ultrasound, ABA and blood gas analysis remain important investigation methods of infants with suspected IHPS and nonbilious vomiting. In the case of severe alkalosis hypercapnia can be expected and hypoventilation may occur. Hypercapnia even can be observed in infants with non-surgical vomiting.

Negative BE values must be interpreted with caution. Base deficit typically occurs in infants with repeated nonsurgical vomiting. However, negative BE does not exclude IHPS.

The clinical importance of hypercapnia and hypoxia in infants with IHPS needs further investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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