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Comparison of analytical performance of i-Smart 300 and pHOx ultra for the accurate determination of pleural fluid pH

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ABSTRACT

Background: Pleural fluid pH is an essential test for diagnosing complicated parapneumonic effusion. We evaluated the performance of two blood gas analyzers in measuring pleural fluid pH.

Methods: The i-STAT G3+ (Abbott) was used as a reference analyzer to evaluate the pH values obtained from other methods: the i-Smart 300 (i-SENS), the pHOx Ultra (Nova Biomedical), using a clot catcher to filter off microclot, and pH indicator paper. Within-device precision was performed using quality control materials. We compared pleural fluid pH (n = 86) by the above methods and analyzed the concordance rate at the level of the medical decision point, pH 7.2.

Results: The within-device coefficient of variations of pH were below 0.1% for all blood gas analyzers tested. The slopes of the regression equations for the i-Smart 300, pHOx Ultra, and pH indicator paper against the reference analyzer were 0.850 (95% confidence interval, CI, 0.800–0.896), 0.714 (95% CI, 0.671–0.766), and 1.105 (95% CI, 0.781–1.581), respectively. The kappa values for the i-Smart 300, pHOx Ultra, and pH indicator paper against the reference analyzer were 0.883 (95% CI, 0.656–1.110), 0.739 (95% CI, 0.393–1.084), and 0.464 (95% CI, 0.102–0.826), respectively.

Conclusions: The i-Smart 300 and pHOx Ultra demonstrated good analytical performance and diagnostic accuracy when determining pleural fluid pH compared with that by the i-STAT G3+, whereas the pH indicator paper showed unsatisfactory results.

1. Introduction

Pleural effusion is the pathological accumulation of pleural fluid resulting from excess fluid production and/or increased transpleural pressure, increased capillary permeability, and impaired lymphatic drainage [1,2]. And it occurs in many pulmonary or systemic diseases such as infection, liver cirrhosis, congestive heart failure, and malignancy [1–4].

For assessment and differential diagnosis of the cause of pleural effusion, pleural fluid pH is one of the most useful indicators [4–8], along with the widely recommended indicators such as total protein, lactate dehydrogenase, and glucose levels. Pleural fluid pH greater than 7.30 is associated with uncomplicated effusion [2,4,6,8,9] and that less than 7.20 is associated with complicated parapneumonic effusion (CPPE), requiring chest tube drainage [1,5,8,10]. Hence, accurate measurement of pleural fluid pH is important. However,

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pH can be influenced by many factors, such as exposure to air, temperature, storage time, and sample quality [4]. Moreover, analytical performance parameters such as precision and accuracy are important for providing reliable results. Blood gas analyzers have previously shown higher analytical and diagnostic performance than pH indicator paper or pH meters [1,6]. Here, we evaluated the diagnostic performance of two blood gas analyzers for measuring pleural pH and compared the results to those from the reference blood gas analyzer and pH indicator paper.

2. Materials and methods

2.1. Analyzers

The i-STAT G3+ (Abbott Point of Care Inc., Abbott Park, IL, USA), a cartridge-based blood gas analyzer, was used as a reference analyzer for comparison with the other three methods. This analyzer previously showed results comparable to those of a validated blood gas analyzer for measuring pleural fluid pH [1]. The i-Smart 300 (i-SENS, Seoul, Korea), a recently introduced cartridge-based blood gas analyzer, was evaluated for comparison. The pHOx Ultra (Nova Biomedical, Waltham, MA, USA), now in use for routine arterial blood gas analysis in our laboratory, and pH indicator paper was also compared. The stated accuracy for measuring pH is ± 0.001 for all blood gas analyzers tested and ± 0.2 for pH indicator paper, and the common measurable range for all methods is from 6.5 to 8.0.

2.2. Study design

From September 2017 to March 2018, a total of 86 specimens were evaluated from in- and out-patient samples obtained from thoracentesis or pigtail catheter drainage and submitted to our clinical laboratory for routine body fluid analysis. Samples were collected directly into the test syringes in the case of pig tail insertion, at least 1.6 mL of pleural fluid was collected anaerobically into two BD Preset heparinized syringes (Beckton Dickinson Co., Plymouth, UK, Catalog no. 364,390), totaling 3.2 mL and immediately submitted to our laboratory within 30 min. In the case of diagnostic thoracentesis, we aspirated in a large thoracentesis syringe and aliquoted into the blood gas syringe promptly. We did not use vacutainer tubes to prevent exposure to air [1,7,11]. The Clot Catcher (Nova Biomedical), a disposable and single-use device designed to filter off microclots or debris, was inserted between the syringe and the blood gas analyzer. Although samples were not transported on ice, they were measured immediately upon arrival to minimize the influence of room temperature. Orders of measuring analyzers for each run were variable depending on the prepared order scheme to prevent order from causing analysis bias.

The within-device imprecision was determined by a brief 5-day study protocol. Each level of quality control (QC) materials was measured in duplicate per run, two runs per each day, and performed on 5 consecutive days [12]. Results of the imprecision study were expressed as mean, standard deviation (SD), and coefficient of variation (CV(%)), and the criterion for acceptance was determined as 0.1% according to the desirable biological variation database specifications on Westgard's webpage [13].

Head-to-head comparison was performed using Passing-Bablok regression [14]. And, to compare the concordance rate for clinical significance, a kappa agreement test was used and the criterion was defined as pH < 7.20 and ≥ 7.20 as a medical decision level indicating the possibility of CPPE [1,4,5]. Analyse-it version 5.01 (Analyse-it Software, Ltd., Leeds, UK) was used for statistical analysis. This study was performed under the authorization of the Institutional Review Board (IRB) of Severance Hospital (IRB no. 1–2017-0032).

3. Results

3.1. Precision

Within-device precision of all three blood gas analyzers was acceptable within 0.1% according to the desirable precision criteria. For the i-STAT G3+, within-device CV(%) at low (pH 7.04) and high levels (pH 7.76) was 0.05% and 0.04%, respectively. For the pHOx Ultra, total CV(%) was 0.03% for all levels (pH 7.13, 7.35, and 7.59). For the i-Smart 300, total CV(%) at low, mid, and high levels (pH 7.13, 7.36 and 7.59, respectively) was 0.09%, 0.08%, and 0.09%, respectively.

3.2. Method comparison

Method comparison results using the Passing-Bablok regression are illustrated in Fig. 1. The slopes of the regression equations for the i-Smart 300, pHOx Ultra, and pH indicator paper were 0.850 (95% confidence interval, CI, 0.800–0.906; correlation coefficient, $r = 0.976$), 0.714 (95% CI, 0.671–0.766; $r = 0.966$), and 1.105 (95% CI, 0.781–1.581; $r = 0.498$), respectively. The concordance rate using the kappa agreement test for the i-Smart 300, pHOx, and pH indicator paper were 0.883 (95% CI, 0.656–1.110), 0.739 (95% CI, 0.393–1.084), and 0.464 (0.102–0.826), respectively (Table 1).

4. Discussion

This study investigated the diagnostic performance of the i-Smart 300, pHOx Ultra, and pH indicator paper using the i-STAT G3+ as a reference analyzer. A precision study of three blood gas analyzers showed good performance with a CV(%) < 0.1%. We also

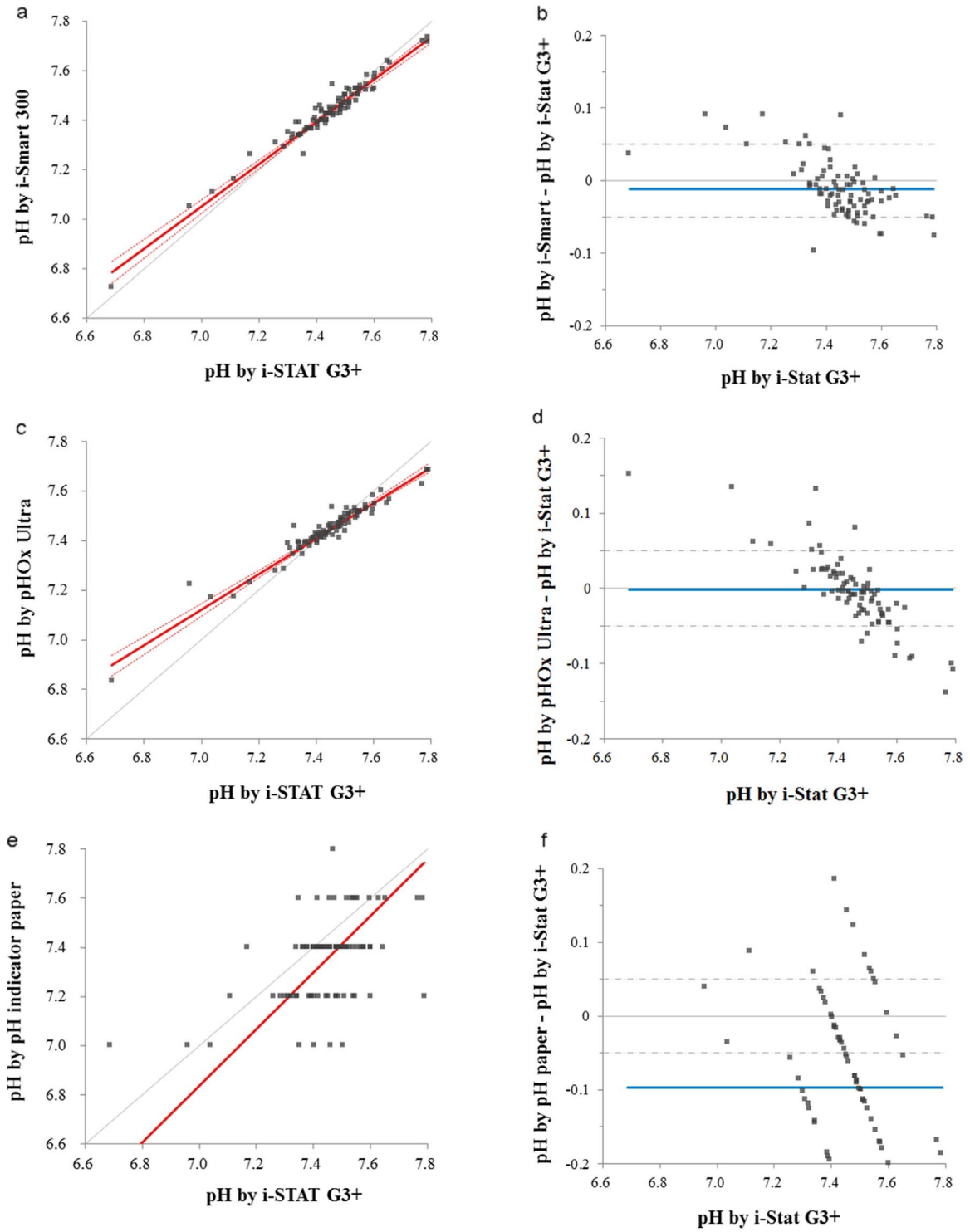

Fig. 1. Scatter Plot with Passing-Bablok regression and Bland-Altman bias plots of pleural fluid pH by the i-Smart 300 (A) and (B), pHOx Ultra (C) and (D), and pH indicator paper (E) and (F), compared with i-STAT G3+ as a reference method. Thick lines represent the Passing-Bablok equations, thin lines represent the identity line, and dashed lines represent the 95% confidence interval.

Table 1
Combined two-by-two tables and kappa agreement test of the pHOx Ultra, i-Smart 300, and pH indicator paper, compared with the i-STAT G3+ as a reference analyzer for diagnosing complicated parapneumonic effusion.

i-STAT G3+ pH	i-Smart 300		pHOx Ultra		pH indicator paper	
	< 7.2	≥7.2	< 7.2	≥7.2	< 7.2	≥7.2
< 7.2	4	1	3	2	3	2
≥7.2	0	81	0	81	4	77
Sum	4	82	3	83	7	79
Kappa[a] Statistics	0.883		0.739		0.464	
(95% CI)	(0.656–1.110)		(0.393–1.084)		(0.102–0.826)	

Abbreviation: CI, confidence interval.
[a] The criterion for assessing clinical concordance was defined as pH < 7.20 and pH ≥ 7.20.

investigated the accuracy for measuring pleural fluid pH using patients' samples. Method comparison was performed using a Passing-Bablok regression. The i-Smart 300 showed good agreement with i-STAT G3+, with a slope of 0.850 (95% CI, 0.800–0.906). The pHOx Ultra showed about 30% lower pH values than the i-STAT G3+. The slope of equation for pH indicator paper was 1.105, with a relatively wide range of 95% CI (0.781–1.581).

A kappa agreement test was performed to assess diagnostic accuracy with pH 7.20 as the medical decision level indicating the possibility of CPPE. The i-Smart 300 and pHOx Ultra showed good agreement as evidenced by high kappa values.

Pleural fluid pH determined by the i-Smart 300 showed excellent analytical agreement with the i-STAT G3+, as the kappa value was greater than 0.80 [15]. The pHOx Ultra was acceptable for diagnosing CPPE at the decision point for pleural fluid pH of 7.20 of less as kappa was greater than 0.6, recognizing an observed bias compared to i-STAT G3+ in this low range. pH indicator paper showed unsatisfactory results (kappa < 0.6) supporting the prior conclusion that it is not suitable for diagnosing CPPE [6,10].

There are limitations to this study. First, we used the i-STAT G3+ as a reference method. Although this analyzer was reported to show results comparable to a validated blood gas analyzer for measuring pleural fluid pH [1], it has not yet been cleared by the Food and Drug Administration (FDA) for measuring pleural fluid pH. According to the FDA website, the ABL 835 Flex Analyzer (Radiometer America Inc., Westlake, OH, USA) and RAPIDPoint 500 System (Siemens Healthineers, Erlangen, Germany) are the only cleared devices for measuring pleural fluid pH [16]. Second, clinical information could not be used to validate CPPE diagnosis, because this study was approved as informed consent-exempt clinical research because pleural fluid samples were de-identified. The studies with a larger sample size or case-control study should be necessary to ensure the usefulness of pleural fluid pH.

Here, we evaluated the analytical performance of blood gas analyzers and pH indicator paper to determine the plausibility of routinely applying these methods in clinical laboratories. The pHOx Ultra and i-Smart 300 were comparable to the i-STAT G3+ for pleural fluid pH determination. If pleural fluid is collected anaerobically in a heparinized syringe and a Clot Catcher is used to filter off possible microclots, these blood gas analyzers can be used to accurately determine pleural fluid pH for diagnosing CPPE.

5. Conclusions

Pleural fluid pH determination using both blood gas analyzers, the i-Smart 300 and pHOx Ultra, is sufficiently accurate for diagnosing CPPE, if pleural fluid is collected anaerobically in a heparinized syringe and a Clot Catcher is used to protect blood gas analyzers.

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Conflict of interest

All the authors declare that there is no conflict of interest.

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