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Suppress or not to suppress gastric acid?

Intra-gastric pH monitoring vs. Litmus paper in critically ill patients

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Abstract

Stress ulceration and gastrointestinal bleeding complicates many clinical illnesses in patients in the intensive care unit (ICU). We hypothesized that suppression of gastric acid and monitoring of gastric pH using intra-gastric pH monitoring can be beneficial to critically ill patients. To test this idea we have performed a pilot study to compare the accuracy of litmus paper to determine gastric pH to a nasogastric platinum-antimony pH probe in a teaching hospital in Tehran. Twenty critically ill patients in intensive care unit who required stress ulcer prophylaxis, by using a crossover design the patients randomized to initially received ranitidine by continuous infusion or intravenous bolus and subsequently were crossed over to the other arm of the study. Gastric pH was determined using pH sensitive litmus paper at the initiation of each arm of the study and at 1, 2, 4 and 8 hours after the initiation of ranitidine. In addition, gastric pH was continuously determined over the same time utilizing a platinum-antimony pH probe made in Iran.

Pilot Results of gastric pH measurement determined with litmus paper and intra-gastric pH probes demonstrated by regression analysis comparing these two methods showed a good correlation between the two methods ($r=0.7$). The pH probe technique for intra-gastric pH measurement appears to be technically simple and clinically applicable for use on patients at risk for stress ulcer bleeding. It may be more accurate than litmus paper in patient receiving H₂ antagonists. Further investigations are needed to validate this idea.

Keywords

Acid Suppression, Gastric pH, Ranitidine, Litmus paper, Stress ulcer, Critical illness

Introduction

Upper GI bleeding related to stress ulcer syndrome, estimated to affect 15% of patients in an ICU, which is associated with increased morbidity and mortality (1). A prospective study of patients admitted to a medical ICU found longer stays and a higher mortality rate (2). Prophylactic therapy for stress ulcers bleeding with antacid or histamine-2 receptor antagonists has shown to decrease

significantly the occurrence of overt bleeding compared with placebo (3-7). Efforts have directed at defining optimal therapy for stress ulcer prophylaxis in high-risk ICU patients. Titration of antacids or H₂ receptor antagonist doses against gastric pH measurements results in optimal prophylaxis. Maintenance of the gastric pH to >3.5 has been recommended but the optimal hydrogen ion level needed to prevent stress ulcer bleeding remains to be determined (3-5,8-12).

The Hypotheses

The Medicines and Healthcare products Regulatory Agency (MHRA) advised that nasogastric (NG) tube position should be confirmed using pH paper. However, gastric pH raised by the use of H₂-blockers and proton-pump inhibitors (PPIs) potentially producing false negative pH. In addition, colorimetric differentiation using pH strips may be more prone to bias than direct pH measurements (11).

Monitoring of intra-gastric pH performed by subjective interpretation of the color change of pH-sensitive paper tested against aspirated gastric juice. Errors in pH measurement of aspirated gastric fluid with pH-sensitive paper may occur because of

- a) Aspiration of residual antacid within the NG-tube,
- b) Provocation of the secretory response by stimulation of duodeno-gastric reflux, c) Removal of gastric contents, which may directly alter the measured pH, or
- d) Misinterpretation of pH paper color changes (8, 12-14).

To increase the accuracy and efficiency of gastric pH, several authors recommended using intra-gastric microelectrodes instead of the standard aspiration technique (6, 15-16). Potential advantages includes decreased handling of gastric juices, ease of measurement, ability to obtain frequent pH readings, and ability to measure pH even in the presence of low gastric volumes (8, 13). More frequent monitoring may allow for prompt detection of pH changes, and therefore expedite changes in therapy. One disadvantage of many continuous intra-gastric pH micro-electrode systems is high cost, which precludes their routine use in all ICU patients at risk for stress ulcer bleeding. Another problem with them is that you need "another NG tube" in the critically ill patient. A single tube that would fill the needs of both an NG tube and an electronic pH monitor would be ideal. We designed and evaluated a recently developed pH-monitoring device in conjunction by Iranian Medical Engineering co. in Tehran, with a pH sensor embedded in the tip of a standard polyvinyl chloride NG tube in ICU patients.

Evaluation of the hypotheses and experimental data

To evaluate our ideas, an experimental study of stress ulcer prophylaxis performed. Patients who

admitted to the ICU and who met our inclusion criteria were entered this pilot study.

Entry criteria included the following: age >18 yrs, a clinical need for a nasogastric tube and stress ulcer prophylaxis, and expectation of 72 hrs of "nothing by mouth" status, a baseline gastric pH <3.5 within 24 hrs of initiation of monitoring and written informed consent as required by our institutional review board.

Exclusion criteria included the following: Pregnant women, use of a H₂-receptor antagonist, within the 8 hours of the study. Use of antacids, or within 4 hours prior to entering the study, hypersensitivity to H₂-receptor blockers, a history of esophageal varices, previous gastric ulcer, surgery, Zollinger-Ellison syndrome, renal failure (a serum Creatinine concentration >3mg/dL), liver enzyme increase (increase in aspartate aminotransferase or alanine aminotransferase concentration greater than times the upper limit of normal), receiving investigational drugs within 30 days, being fed by enteral nutrition, or receiving nonsteroidal anti-inflammatory agents.

Experimental Method

A naso-gastric tube with pH probe was inserted into the stomach. Its position was confirmed by the routine daily chest radiographs. A silver-silver chloride reference electrode was attached to the patient's skin and connected to an electronic digital multi-meter and pH values of 1.0 and 4.0 (fisher scientific, Pittsburgh, PA) and demonstrated a uniform response (mV/pH). Sensitivity, linearity, and reproducibility between sensors determined by the manufacturer to be $-57 \text{ mV} / \text{pH}$, $\pm 0.2 \text{ pH}$, and $\pm 0.1 \text{ pH}$, respectively.

Brief Description of designed experimental pH probe:

Theoretical background on Redox electrode:

Redox electrode – This is like a battery that output current is variable with changes in acidity of solution. Redox electrode is capable of absorbing or releasing electrons. Suitable materials: Metals, which do not react with the constituents of the solution. In addition, we needed a conventional reference electrode Such as combination Redox electrode, which is mostly recommended. Potentiometric methods: We needed an mV-Transmitter with a high impedance input (pH transmitter with mV input). We followed the Nernst's Law.

Nernst's law:

$$E = E_0 + \frac{2,303 \times R \times T}{Z \times F} \log \frac{[Ox]}{[Red]}$$

A Redox electrode is not an ion sensitive electrode and concentration determination of a particular substance is only possible if other factors are constant. As a result, we used Ag/AgCl electrode for easier handling:

E of Ag/AgCl in 3 mol KCl/l = + 207 mV

Exchange current density "*The kinetic model*":

$I = I_0 / A$ [A/m²] At equilibrium E_0 exchange current density $I_0 = I_+ = I_-$

Conductivity defined as the ability of a solution to conduct current.

The amount of current flowing is roughly proportional to the number of ions present in the conducting solution.

Conductivity measurement gives information about the total ionic content of all ions in a solution. The measured conductivity depends on both the dimensions of, and the distance between, the electrodes. This leads to considerable complications for comparative measurements. To avoid this problem, the concept of "Specific Conductivity" been introduced. Specific conductivity is denoted by C and can be determined from the conductance G and the value

$$L/A: C = G * L/A$$

C = Conductivity [S/cm]

G = Conductance [S]

L = Distance between electrodes [cm]

A = Area of electrode [cm²]

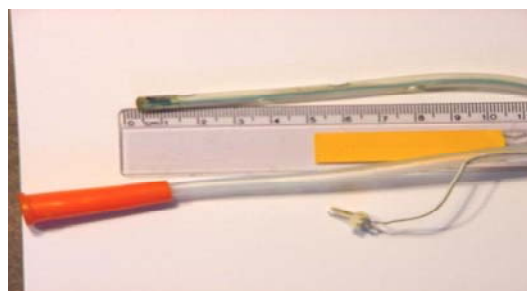


Figure 1. Picture of the nasogastric tube designed for measuring gastric pH



Figure 2. Picture of digital pH monitor

Table 1. Patients' Demographic information

| Patient No. | Gender | Age (Yr) | Weight (Kg) | Basal 'gastric pH |
|-------------|--------|----------|-------------|-------------------|
| 1 | Female | 24 | 60 | 3.2 |
| 2 | Male | 27 | 70 | 3.4 |
| 3 | Female | 30 | 65 | 3.0 |
| 4 | Female | 24 | 62 | 2.5 |
| 5 | Female | 54 | 70 | 1.8 |
| 6 | Female | 42 | 65 | 1.4 |
| 7 | Male | 69 | 60 | 3.2 |
| 8 | Male | 70 | 62 | 2.0 |
| 9 | Male | 62 | 60 | 2.4 |
| 10 | Male | 64 | 75 | 1.24 |
| 11 | Female | 58 | 70 | 0.99 |
| 12 | Male | 28 | 65 | 1.22 |
| 13 | Female | 26 | 60 | 1.06 |
| 14 | Male | 56 | 67 | 2.09 |
| 15 | Female | 47 | 70 | 1.54 |
| 16 | Female | 42 | 65 | 2.4 |
| 17 | Male | 65 | 60 | 2.8 |
| 18 | Female | 57 | 68 | 2.9 |
| 19 | Male | 60 | 70 | 2.7 |
| 20 | Female | 52 | 60 | 2.2 |
| Mean | - | 48 | 65.25 | 2.20 |
| SD | - | 16.24 | 4.59 | 0.77 |

In our experimental and pilot study of Litmus paper for measuring the gastric pH, 5 ml of gastric juice aspirated from the nasogastric tube for determination of the pH-utilizing litmus paper (Merck, Germany). Patients were randomized and started on stress ulcer prophylaxis with either continuous of bolus H₂ receptor antagonist therapy when their gastric pH decreased to <2.5 the patient's pH was determined simultaneously using both methods at the initiation of drug therapy and at 1, 2, 4 and 8 hrs. After 16-hr washout period, patient subsequently crossed over to the other arm of the study. Once again, simultaneous pH determination made for each patient. Thus, ten paired pH determination made for each patient. Correlation between litmus pH determinations and intra-gastric pH probe values performed, using statistical packages implemented on a computer. Concordance between the two methods tested with Mc Nemer's test. A p<0.05 was accepted as significant. Summary of statistics presented as mean ±SD unless otherwise noted. Bias, mean difference between the measurements, was determined by the method of bland and Altman (11). Twenty patients (nine male, 11 female: mean

age \pm SD 4.800 ± 16.24 years) were enrolled in our pilot study. The demographic information on them was described in table 1.

Pilot Results

Fig.3 shows the results of metered vs. litmus paper determined pH ($r^2=0.94$, $p<0.01$, 95% confidence interval = -0.155 to 0.176). Gastric pH measurements that were determined with litmus paper and those measurements obtained using intra-gastric pH probes demonstrated an excellent correlation ($r^2 = 0.94$, $p<0.01$) (Fig. 3). Bias was determined to be 0.01 with 95% confidence interval of -0.155 to 0.176. Only two paired samples demonstrated a clinically relevant discrepancy, differing by >1 pH unit. In one case, the litmus paper pH value was 2.0 while the metered pH value was 4.5. In the other example, the metered pH was 4.0 while the litmus paper pH was 6. Using metered pH as the reference standard, litmus paper pH determination on aspirated gastric contents was 97% sensitive and 98% specific for the need for alkalization of the stomach. McNemers test of correlated proportions could not demonstrate a significant difference between the two monitoring methods (chi-square = 0.5, $p>0.48$), and the kappa statistic (0.95, $p<0.001$) demonstrated "excellent" concordance.

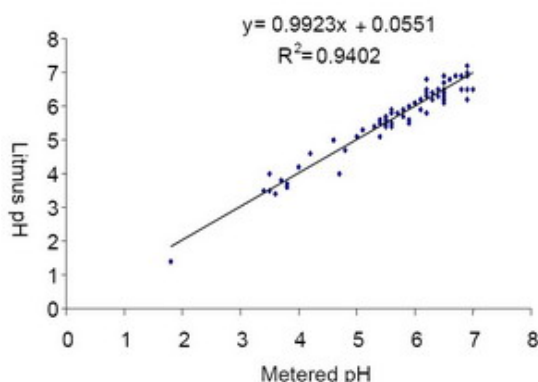


Figure 3. Result of metered vs. Litmus paper determined pH

Discussion

The term stress-related mucosal disease (SRMD) represents a conditions ranging from stress-related injury (superficial mucosal damage) to stress ulcers (focal deep mucosal damage) caused by mucosal ischemia.

SRMD is seen in critically ill patients in the intensive care unit (ICU). Clinical studies demonstrated that a low intra-gastric pH value is an

important determinant of stress ulceration and that fixed dose empiric therapy cannot assure appropriate pH control (6-7). Simple and accurate on-demand measurements of intra-gastric pH may be a desirable goal in the clinical management of patients at high-risk for the development of stress ulcer bleeding. The micro-electrode systems presently available would appear too expensive for routine use in the ICU and their only value is to monitor intra-gastric pH. Since many patients in an ICU setting require a NG tube for either decompression delivery of medication, it seems logical for a pH micro-electrode to be combined with this tube. The advantages include reduction in the number of tubes passed into the stomach, improved patient comfort, and the possibility of decreased tube-related esophagitis. A single tube would provide long-term pH monitoring and gastric feeding/decompression. An additional advantage of the combination pH probe-NG tube is the ability to obtain measurements without handling gastric secretions, which would decrease exposure of hospital personnel to potentially infectious agents. The new technique for obtaining intra-gastric pH measurements appears technically simpler, clinically applicable, and may be more accurate than conventional monitoring of gastric contents by aspiration and testing with pH paper.

We noted higher individual patient mean gastric pH values for 15 of 20 patients in whom the pH obtained by the aspiration/pH paper methods compared with the probe method when antacid where used. Other investigator (16-25) have been documented this difference in pH values between two pH-testing methods. We noted as did Meiners et al, that the discrepancy between the gastric aspirate pH and the intra-gastric pH electrode was not present in patients who received and IV H₂ receptor antagonist, although the number of data points in this pilot study was relatively small (15). One study evaluated antacid prophylaxis for the prevention of upper GI bleeding in critically ill patients (24). Therefore, if the success of treatment depends on accurate intra-gastric pH measurement, then the probe method may be preferable to the conventional aspiration method. In a study by Lugo et al, concluded that gastric pH and should be monitored by nasogastric pH probe and the dose of ranitidine adjusted accordingly (25). In another study, continuous infusion of ranitidine was more effective than administration of an equivalent dose of the drug by bolus in maintaining the appropriate gastric pH required for the prevention of stress ulceration by using intra-gastric pH-probe (26). The interpretation of gastric pH using pH-sensitive paper is subjective and dependent on the ranges and visual increments provided by the pH paper manufacturer.

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