Abstract

Background and objective. A new catheter-free outpatient oesophageal pH-meter system (Bravo®), has recently been developed. The objective of this study is to test the tolerance, safety and efficacy of the system in the measurement of gastric-oesophageal reflux by comparing it with a conventional pH system.

Patients and method. The study was performed on a control group consisting of 10 healthy volunteers (group 1) and in a group of 40 patients with symptoms of gastric-oesophageal reflux disease (groups 2 and 3). An upper digestive system endoscopy, oesophageal manometry and oesophageal pH measurements with a conventional system and/or with the Bravo® catheter-free system, was performed on all patients. All patients who had both tests done (groups 1 and 2) filled in a questionnaire on any physical problems and changes in their daily activity.

Results. The test tolerance was higher with the Bravo® system in 9 parameters studied. In the group of healthy volunteers (group 1), the median (range) of the total percentage of pH<4 was 1.1% (0.5-3.1) with the conventional pH and 1.7% (0-3.4) with the Bravo®. When comparing the patients with symptoms of gastric-oesophageal reflux disease (group 2) with those who had only one type of pH measurement made, the acid reflux was significantly higher in patients with Barrett’s oesophagus than in the rest of the groups, with conventional pH as well as with the Bravo®. If we analyse the patient group with disease due to gastric-oesophageal reflux with those on whom both techniques were used (group 3), 7 of the 10 patients had a pathological reflux that only showed up on measuring pH with the Bravo® system.

Conclusions. Catheter-free pH measurements (Bravo®) is better tolerated and with better satisfaction for the healthy volunteers and patients than with conventional PH, even, on occasions being more efficient for studying acid reflux due to the lower incidence of negative results.

Key words: pH monitoring. Esophagus. Gastroesophageal reflux. Bravo.
Introduction

Twenty-four hour outpatient monitoring of oesophageal pH is the standard method for quantifying acid reflux as it is the most specific and sensitive, and it has shown a good correlation with the severity of the symptoms and endoscopic injuries. It has also been proven very useful for checking the efficacy of medical and surgical treatments for gastroesophageal reflux disease (GERD).²

Initially, studies into oesophageal pH were carried out in a motility laboratory which required a complex use of infrastructure and the use of pH crystal catheters for measuring oesophageal acid. Acid reflux measurements could be carried out for 24 hours afterwards, but always inside the motility laboratory. In 1974, Johnson et al. described the most representative pH-monitoring parameters for the study of pathological oesophageal acid reflux. During the 1980s, the introduction of analogical to digital data converters allowed the storage of a higher number of results in portable units, and since then this exploration has been carried out in outpatients departments. However, despite this improvement in technology, the traditional method continues to require a catheter being passed through the nose and down the oesophagus with the discomfort of having to remain in this position for 24 hours, linked up to an external system which collects and records the required data. This system can cause nose and throat discomfort, rhinorrhea, cephalalgia, odynophagia, and certain social discomfort. All of these inconveniences limit daily activity and the ingestion of foods, conditioning the lifestyle of the patient over the course of the study and even negatively affecting it. This inconvenience, a new system of outpatient monitoring of oesophageal pH is being used which does not require the use of a permanent catheter to study pH levels. The Bravo® system (Medtronic Inc., Shoreview, United States) consists of a measuring capsule which is inserted in the oesophagus. It measures the pH level and transmits the data by radiotelemetry to a receiver. This system has been previously tested on animals and in clinical studies in control groups using healthy volunteers. Others authors have published their experiences with a technology similar to Bravo® for studying gastric function and oesophageal pH.³

The aim of this study is to check the tolerance, safety, and efficacy of the catheter-free pH-monitoring system with radiotelemetry (Bravo®) in the measurement of gastrooesophageal reflux and to compare it with conventional pH measuring systems.

Patients and Method

This study included 10 healthy volunteers and 40 patients with GERD who were grouped as follows:

- Group 1. Both types of pH-monitoring were carried out on the 10 healthy volunteers (average age, 27 [range, 25-59], 5 males and 5 females). The pH results were compared for both methods, as were the degree of satisfaction, the level of discomfort, and alterations to daily activities.
- Group 2. Thirty of the patients with GERD symptoms were divided into 3 subgroups according to endoscopic findings: A: 10 no oesophagitis; B: 10 with I-II oesophagitis with no Barrett’s oesophagitis (BO); and C: 10 with Barrett’s oesophagitis. Half the patients in each group underwent standard pH-monitoring (n=15; 45 years of age [17-73], 9 males and 6 females) and the other half were monitored with the Bravo® system (n=15; 37 years of age [21-59], 8 males and 7 females).
- Group 3. The remaining 10 patients (36.5-year-old [18-56], 7 males and 3 females) who had shown clear symptoms of GERD and a normal or borderline on normal oesophageal pH level with the standard monitoring system were re-tested with the Bravo® system to confirm whether or not they had acid reflux. The endoscopic findings in these 10 patients were as follows: 4 patients with I-II oesophagitis, 4 patients with BO, and 2 patients with no oesophageal lesions. The degree of satisfaction, discomfort and alterations to daily activity were also recorded for these patients.

Inclusion Criteria

- General criteria: over the age of 18, informed consent of the risks, benefits and alternative diagnostic tests, committed to completing the follow-up protocol.
- Control group: fewer than 2 episodes of pyrosis or regurgitation per month, no dysphagia or other atypical reflux symptoms, no oesophageal motility disorders, not taken medication for acid reflux (proton pump inhibitors, antih2 and prokinetics). All patients had an upper endoscopy of the digestive tract which showed no evidence of a hiatal hernia or oesophagitis.
- Patient group: typical reflux symptoms (pyrosis and/or regurgitation) – Group 1: both types of pH-monitoring were carried out on the 10 healthy volunteers (average age, 27 [range, 25-59], 5 males and 5 females). The pH results were compared for both methods, as were the degree of satisfaction, the level of discomfort, and alterations to daily activities.
- Group 2. Thirty of the patients with GERD symptoms were divided into 3 subgroups according to endoscopic findings: A: 10 no oesophagitis; B: 10 with I-II oesophagitis with no Barrett’s oesophagitis (BO); and C: 10 with Barrett’s oesophagitis. Half the patients in each group underwent standard pH-monitoring (n=15; 45 years of age [17-73], 9 males and 6 females) and the other half were monitored with the Bravo® system (n=15; 37 years of age [21-59], 8 males and 7 females).
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Exclusion Criteria

The following patients were excluded from the test: those under 18 years of age, those with oesophageal stenosis, oesophageal varix, any type of lesion affecting the nostrils, severe oesophageal motor disorders, high anaesthetic risk (ASA IV), previous history of coagulopathy, haemorrhage, intake of anticoagulants or platelet antiaggregates, history of myocardial infarction or cerebrovascular accident in the 6 months before the study, pregnant, history of radiotherapy in the thoracic region, history of digestive haemorrhage in the 6 months prior to the study, any known medical disorder which could alter the data in the study, unable to accept all the study protocols.
Endoscopy of the Upper Digestive Tract

An endoscopy of the upper digestive tract was carried out on all the subjects to assess the presence of oesophageal inflammatory lesions (Savary-Miller10), metaplastic epithelium, oesophageal varix, oesophageal stenosis or any other oesophageal or pharyngeal lesions which could complicate the study and which could lead to complications for the patient or volunteer.

Stationary Oesophageal Manometry

A stationary oesophageal manometry was carried out on each subject to exactly identify the location of the inferior oesophageal sphincter (IOS). A continuous perfusion 4-electrode catheter was used for the manometry with a hydropneumo-capillary perfusion pump (JS Biomedicals Inc., Ventura, CA, United States) and a polygraph (Synectics Medical, Stockholm, Sweden) connected to a personal computer. The technique has been described in previous studies.11

Conventional pH-Monitoring

For those patients selected to be monitored with the conventional ph-monitoring, the procedure was carried out using a Digitrapper Mark III ph-monitoring (Synectics, Stockholm, Sweden) and a pH catheter with an antimony electrode placed 5 cm above the upper edge of the IOS, which itself had previously located with an oesophageal manometry. For both the conventional ph-monitoring and the Bravo® system the pH electrodes were calibrated in pH 7 and pH 1 buffers, and GORD medication was withdrawn from the patients at least 1 week before the study. The results obtained were analysed by a computer programme (Esophogram Gastrosoft, Irving, United States, CA, United States) and a polygraph (Synectics Medical, Stockholm, Sweden) connected to a personal computer. The technique has been described in previous studies.11

Radiotelemetry-pH-Monitoring (Bravo®)

For the patients and volunteers selected for the catheter-free pH-monitoring this was carried out with a radiotelemetry ph-monitoring known as the Bravo® system (Medtronics, IN., Shoreview, United States). It consists of a small measuring capsule (25 mm × 6 mm × 5.5 mm) (Figure 1) which contains an antimony pH electrode, a radio-transmitter and a battery. It measures the pH in the oesophagus every 6 seconds and every 12 seconds it transmits the pH data to a receiving unit via radio waves. The delivery device for putting the capsule in place (Figure 2) has the capsule attached to its distal side and a connection device for applying suction attached to its proximal side. This is then inserted nasally or orally. Once the distal side of the delivery device is in place, 5 cm above the upper border of the IOS (previously located with a manometry, negative pressure is applied with a suction device connected to the proximal side of the delivery device which applies suction to a section of the oesophageal mucosa through a 3.5 mm orifice in the capsule. A device then inserts a small needle in place, thereby fixing the capsule to the mucosa. The introduction of the delivery device and the placement of the capsule are mostly carried out without the need for a simultaneous endoscopy. In previous studies carried out in the Surgery Department of the University of Southern Carolina,16 the percentage of cases in which the capsule was attached correctly to the mucosa was 97%. Once the capsule is in place, it begins to register and transmit a signal to the receiver (Figure 2), which is a small device (100 mm × 70 mm × 30 mm and weighing 165 grams) which can be fixed to a belt, with a small screen where the pH value is displayed. The test was carried out over 48 consecutive hours in a outpatient departments. It also requires keeping a record of meal times and supine position. This is also the case with the conventional ph-monitoring system. After 48 hours the patient or the volunteer returns to the motility laboratory to return the receiver and the diary they have kept. The receiver transmits the data to a personal computer using infrared rays. A software programme is then used to analyse the data following the Johnson and DeMeester methodologies, as is also the case with the conventional ph-monitoring (Figure 3A and B). For all patients using the Bravo® system, a simple radiograph of the thorax and abdomen was carried out after 7 days to check that the capsule had been expelled. This was repeated at 15 days if required (Figure 4A and B), as mentioned by previous authors.5,7,12 All the patients completed a questionnaire (Figure 5) about any possible physical problems (nasal, pharyngeal, thoracic), or alterations to their daily life, moods, sleep pattern, or meals, as well as their degree of satisfaction with the test carried out. In total, 10 parameters were tested with 5 options each (1=none [problems or alterations], 2=few, 3=moderate, 4=a lot, 5=unbearable problems or complete alterations to daily activity).

Statistical Analysis

All the data was analysed using the SPSS 14 computer programme (SPSS, Inc. Chicago, Illinois, United States). The average, median and range were taken for all the data. The comparison between the results of the subjective assessment of both test types on the volunteers (group 1) and the patients with GORD from group 3 were carried out using the Wilcoxon statistical test. The percentages of the study of pH-measurement with both systems were compared using the t-student statistical method. A P value less than .05 was considered significant.

This study was carried out with the authorisation of our hospital’s Ethical Committee and Research Committee.
Results

Placement and Expulsion of Bravo®,

The device was inserted nasally in 25 patients and orally in 10. This was the preference for the latter patients as they were more tolerant to it and found it easier. In these 10 patients, the manometry was also carried out orally. Three patients experienced a failure in the placement of the Bravo® capsule as it was incorrectly inserted in the oesophageal mucosa. In 2 patients the capsule fell into the stomach, and in the third patient, the capsule was immediately vomited back up. Insertion was reattempted 15 days later for the first 2 patients. All the patients excreted the capsule in the 15 days following the test.

Group 1: Control Group

In the group of healthy volunteers, there were significant differences in the subjective assessment of both tests (P<.05) (Figure 6); a lower score was recorded (less problems or alterations to daily activity) for the catheter-free ph-monitoring (Bravo®) in 9 of the 10 parameters studied. Thoracic discomfort was higher with the Bravo® system (not statistically significant). Adding all the scores up from the 10 parameters (minimum 10 points = no problems, maximum 50 points = unbearable), gives an average of 24 points (16-29) in the conventional ph-monitoring system, and 12 points (11-15) with the Bravo® system (P=.01); there was generally a higher level of satisfaction with the Bravo® system than the conventional ph-monitoring system. All the volunteers in the control group chose the Bravo® system as being the most tolerated choice should they have to repeat the test.

As can be seen in Table, the measuring time was longer in Bravo® than in the conventional ph-monitoring test as it was done over a 48 hour period. However there were no differences in either method with regards to the quantification of the total percentage of time with pH<4 (1.1% with the conventional pH test and 1.7% with the Bravo® test), keeping in mind that both tests were carried out on the same subjects. The 95 percentile was 2.7 in the conventional test and 2.9% in the Bravo® test.

Group 2: Patients With GORD

Table shows the results from the oesophageal pH test using both systems on each one of the subgroups with patients with GORD. It can be seen that with both the conventional ph-monitoring and the Bravo® system, acid
Reflux was significantly higher \( P<.05 \) in those patients with BO (subgroup C) than in those with oesophagitis with no BO (subgroup B) and in the patients with symptoms of gastro-oesophageal reflux without inflammatory lesions (subgroup A), although we cannot compare between both techniques in these groups as they were carried out on different patients.

Lastly, we did compare the results from the first 24 hours, the second 24 hours and the total results with the Bravo® system in patients with GORD (group 2). We could see that in 4 of the 15 patients (27%) there were discrepancies between the 2 days of monitoring and the final results, what let us observe 4 patients showing pathological acid reflux that would have a negative result in a conventional 24 hour pH-monitoring system.

**Group 3: Patients With GORD and a Negative Conventional pH**

We noticed a higher period of time with pH<4 in the results from the Bravo® studies (8.8%; 0.7-16.7) than with the conventional pH-monitoring results (4.1%; 0.8-4.5), with significant differences \( P<.001 \). In total, 7 of the 10 patients had pathological reflux which was only seen when measuring pH using the Bravo® system (Figure 7). As with the control group, the degree of satisfaction with the Bravo® system was significantly higher than with the conventional pH-monitoring system (Figure 6).

**Discussion**

Our results show that carrying out outpatients catheter-free oesophageal pH monitoring with the Bravo® system is of great benefit to the patient and their tolerance to the test, and it also provides more reliable results. All the patients who took both tests (conventional pH-monitoring and Bravo® system) preferred the catheter-free pH-monitoring system, showing significant differences between the 2. The Bravo® system causes less nasal and pharyngeal discomfort for the patient, it barely alters the patient’s daily activities and it allows them to carry out their work normally and to have a normal diet without any restrictions. These patients did frequently refer to the feeling of having a foreign body inside them and to a mild and transitory thoracic pain, above all in relation to the capsule being put in place in the oesophageal mucosa, and they also referred to a slight oesophageal motor disturbance occurring in the area where the capsule was located.\(^\text{12}\)
The method for inserting the capsule varies from author to author. Some\textsuperscript{13-15} place it using an endoscopy to locate the squamocolumnar junction of the oesophageal and gastric epithelium as a reference, and then the capsule is inserted 6 cm above this, this point coincides with manometry referencing. Therefore, an endoscopy needs to be carried out, generally under sedation which increases the expense of carrying out an outpatients pH-test. Also, in those patients with Barrett’s oesophagitis, as the union of the epitheliums is raised by the metaplasia, some of the points of reference are missed and it is almost impossible to securely place the capsule. However, in patients who undergo a simultaneous endoscopy as part of the investigation into their oesophageal disorder, it can be useful to put the Bravo\textsuperscript{®} capsule in place at this stage. With regards to our study, and as is the case with other authors,\textsuperscript{6} we prefer to place the electrode 5 cm above this reference point. Usually, most manometers and Bravo\textsuperscript{®} positioning devices are inserted nasally. Occasionally, due to the size of the capsule and/or disorder in the nostril, insertion can be painful and in some cases, traumatic with mild epistaxis. However, if the manometric monitoring of the IOS is carried out orally then the Bravo\textsuperscript{®} positioning device can be inserted more easily and quickly through the mouth with less nausea. This method was used in 10 patients from our study and is currently the process of choice.\textsuperscript{16}

The Bravo\textsuperscript{®} system safe and well tolerated. So far no serious complications have been recorded in relation to its placement. The capsule is not inserted very deeply (3 mm), almost like an endoscopic biopsy so there is virtually no risk of perforation. Possible oesophageal haemorrhaging is also not an issue in the puncture area if logical precautions are taken such as contraindication in patients with oesophageal varix and extrinsic (anticoagulants or antiaggregants) or intrinsic coagulation. The capsule generally detaches in 3-5 days, although in some patients it can take longer than a week and it is advisable to carry out a radiography of the thorax after 7 days to check. If after 15 days the capsule has not become detached or there is any unbearable thoracic pain, it is advisable to carry out an endoscopy to extract the capsule. This has not been necessary in any of our patients, but other authors\textsuperscript{13} have communicated existing cases. Also, none of our patients experienced the capsule becoming blocked in any section of the gastrointestinal tract after its detachment and during its expulsion. For extra safety it could be advisable to carry out an abdominal radiograph (Figure 5B) to check that it has been expelled.

1. Have you experienced any discomfort in the nose during the test?
   None (1) A little (2) Average (3) A lot (4) Unbearable (5)

2. Have you experienced any discomfort in the throat during the test?
   None (1) A little (2) Average (3) A lot (4) Completely (5)

3. Have you experienced any discomfort in the chest during the test?
   None (1) A little (2) Average (3) A lot (4) Completely (5)

4. Did the test alter your physical activity? (walking, gym, sport, etc)
   None (1) A little (2) Average (3) A lot (4) Completely (5)

5. Did the test alter your daily meals? (type of food, quantity, drinks, etc)
   None (1) A little (2) Average (3) A lot (4) Completely (5)

6. Did the test alter your sleep pattern? (Did you sleep more/less hours, or worse?)
   None (1) A little (2) Average (3) A lot (4) Completely (5)

7. Did the test alter your ability to work (hours, concentration, difficulties, etc)
   None (1) A little (2) Average (3) A lot (4) Completely (5)

8. Did the test alter your mental state or your mood?
   None (1) A little (2) Average (3) A lot (4) Completely (5)

9. In general, did the test alter your daily life?
   None (1) A little (2) Average (3) A lot (4) Completely (5)

10. Your overall degree of satisfaction with the test is:
    Very satisfied (1) Satisfied (2) Average (3) Dissatisfied (4) Very dissatisfied (5)

Figure 5. Individual questionnaire on tolerance, satisfaction, and modifications to daily life with the pH-monitoring.
However, although pH-monitoring with the Bravo® is safe and well tolerated by patients, it should also be pointed out that it is just as efficient as the conventional pH-monitoring system in the quantification of oesophageal acid reflux. Pandolfino et al. have carried out simultaneous studies of oesophageal pH in healthy volunteers with the Bravo® and conventional pH-monitoring systems and they have recorded some discrepancies in the measurements taken with both systems due to problems of thermal calibration, which were then resolved by modifying the software (Polygram Net, Medtonic, Inc.). Either way, it is necessary to establish some normal values of oesophageal acid reflux with the Bravo® system which can be used as a reference for the scientific community as a whole.

From our results we can see that in group 2, the reflux quantified using the Bravo® system increased depending on the severity of oesophageal lesions which were much more prevalent in patients with BO (subgroup C), the same happened in a different group of patients who underwent the study with a conventional pH-monitoring. Other authors have shown that the Bravo® system is more efficient than the conventional pH-monitoring method as the pH recordings are not altered by modifications to daily activities or diet. On occasion, when monitoring pH with an outpatients oesophageal pH-monitoring on a patient with typical symptoms of gastro-oesophageal reflux (pyrosis and acid regurgitation) the results have shown that there is no pathological acid reflux (pH<4 with regards to the total <4.5%). In these cases the negative result can be explained by various circumstances: a) it can happen that the symptoms are due to reflux with a high biliary content; in this case outpatient monitoring of oesophageal bilirubin (Bilitec®) or...
oesophageal impedance testing can be diagnostic; b) symptoms can be caused by visceral hypersensitivity or by a gastric or biliary disorder in which case other diagnostic tests need to be carried out for confirmation; c) it could be the case of a false negative recorded due to significant modification in the habitual activity and diet of the patient which resulted in the test showing that the patient did not have reflux on that day or that it was under-recorded; and d) lastly the negative results could be because reflux varies in the same individual from one day to the next and on the day of the pH-monitoring the patient did not show any signs of pathological reflux. In these last 2 cases, carrying out catheter-free pH monitoring with the Bravo® system could be very useful and could clarify the diagnosis. In the current study the group of 10 patients with GORD all had negative pH results with conventional pH-monitoring (group 3). This group was re-tested with the Bravo® system and evidence of pathological reflux was shown in only 7 of those patients. To explain this “recovery” in these patients with negative results in the initial pH-testing it can be seen that the results of the questionnaire on test-tolerance and quality of life which the patients answered subjectively, are significantly better when carrying using the Bravo® system. In other words the Bravo® system is more accepted and does not affect daily activities.

On the other hand, this new system is currently more expensive as the pH-monitoring capsule (Bravo®) can only be used once and the related technology increases its price. The cost is compensated by the efficacy of the study and the possibility for the patient to completely carry out their normal lives without any inconveniences or discomfort.

To conclude, patients have a much better tolerance of the new system of outpatient monitoring of pH using a catheter-free pH meter (Bravo® system) than of the conventional pH-monitoring. It alters their daily life less and therefore it decreases the number of negative results and is therefore put forward as an efficient alternative to conventional oesophageal motility studies.

References