UNIVERSITY OF CINCINNATI

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I, Jose M Garza, hereby submit this original work as part of the requirements for the degree of:

Master of Science

in Clinical and Translational Research

It is entitled:

Evaluation of acid suppression medications, symptoms and type of feeding in infants suspected of gastroesophageal reflux utilizing pH-impedance monitoring

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This work and its defense approved by:

Committee Chair: Erin Nicole Haynes, DrPH

Mitchell Cohen, MD

Ajay Kaul, MD
Evaluation of acid suppression medications, symptoms and type of feeding in infants suspected of gastroesophageal reflux utilizing pH-impedance monitoring

A thesis submitted to the
Graduate School
of the University of Cincinnati
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requirements for the degree of

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by

Jose M Garza
M.D. Universidad Anahuac

May 2010

Committee Chair: Erin Haynes DrPH
Abstract

Introduction: Gastroesophageal reflux (GER) occurs more frequently in infants compared to older children. Reflux episodes in most infants are considered to be physiologic. Yet many infants are diagnosed with gastroesophageal reflux disease (GERD) and empirically treated with acid suppression medications due to non-specific symptoms.

Methods: Combined pH-multichannel intraluminal impedance (pH-MII) studies were retrospectively reviewed in 186 infants. We evaluated GER characteristics to compare those infants on ranitidine, lansoprazole and no medications; investigated if the method of feeding (oral, nasogastric or gastrostomy) is associated with GER, and by using logistic regression and negative binomial distribution we evaluated which symptoms are associated with GER.

Results: There was no difference in the total number of reflux events or number of proximal reflux events between the medication groups. Infants receiving lansoprazole had significantly fewer number of acid reflux events (p<0.0001), but there was no difference in the number of acid reflux events between infants receiving ranitidine or those on no acid suppression medication. A total of 4159 symptoms were recorded during the studies; 1504 (36%) were associated with a reflux event and only 369 (9%) were associated with an acid reflux event. When total number of reflux episodes and events are taken into consideration, acid reflux episodes are as likely to be associated with a symptom as non acid events (p=0.66). The NG fed group had less total reflux episodes when compared to the PO fed group (p=0.012) and no difference was seen when compared to the GT fed group (p=0.64). In the NG tube fed group there was no difference the number of total (p=0.84), proximal (p=0.29) or acid (p=0.31) reflux events between those infants fed NG continuously and those fed by NG bolus.

Conclusion: Most of the attributable of GERD in infants such as cough, gagging, pain and desaturation are less likely to be associated with a reflux event and have very poor symptom correlation to reflux. In those patients for which an association exists, non-acid episodes are as likely to cause symptoms as acid reflux episodes. If the symptoms are still suspected to be due to GERD, a combined pH-impedance study may be indicated before putting the infant on long-term acid suppression therapy.
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Introduction

Gastroesophageal reflux (GER) occurs more frequently in infants compared to older children. Reflux episodes in most infants are considered to be physiologic. Yet many infants are diagnosed with gastroesophageal reflux disease (GERD) and empirically treated with acid suppression medications. The diagnosis of GERD is also made in neonatal intensive care units based on a variety of nonspecific complaints and has been associated with longer hospital stays and higher hospital costs. Infants with presumed GERD are either prescribed a histamine 2 receptor blocker (H2RB) or a proton pump inhibitor (PPI) based on physician practice or insurance coverage. PPI use in infants is estimated to have increased up to 7-fold between 1999 and 2004, despite the fact that there is limited quality data on their pharmacokinetics and efficacy in reducing acid reflux episodes and symptoms in infants. Additionally, there are no studies that compare the effect of H2RBs and PPIs on GER characteristics and symptoms in infants.

Amongst the PPIs, omeprazole was shown to be effective in reducing acid exposure in premature infants with pathological acid reflux utilizing pH probe. However, in another study the impact of lansoprazole on symptoms attributable to GERD in infants was found to be no different from placebo. These studies agree with another double-blind placebo controlled trial which found that although omeprazole significantly reduced esophageal acid exposure it did not have an effect on irritability.

Several clinically relevant issues need to be addressed including: what is the normal GER profile in infants; which specific symptoms are associated with reflux episodes in infants; does acid suppression resolve these symptoms; and which pharmacologic agent is most effective and safe in accomplishing these goals. Invasive measuring of GER data from a large number of normal infants is challenging due to obvious ethical reasons. Most infant studies thus far have been
performed on small numbers of subjects and have used pH monitoring as a means of evaluating GER. The newer combined pH-impedance technology has been shown to increase detection of both acid and non-acid reflux events and improve clinical correlation of reflux events with symptoms. Furthermore, this technology can also be utilized to study the change in GER profile as a result of acid suppression in infants.

Utilizing our institutional pH-impedance database we evaluated GER characteristics in infants suspected of having reflux-related symptoms specifically to evaluate if infants on acid suppression medications have significantly fewer acid reflux episodes than those on no medication. We also evaluated which symptoms are associated with GER in infants and if the method of feeding (oral, nasogastric or gastrostomy) is associated with GER.

Methods

Study Population

All combined pH-multichannel intraluminal impedance (MII) studies performed in infants at Cincinnati Children’s Hospital Medical Center were retrospectively reviewed and a total of 241 infant studies were identified between January 2002 and June 2009. All those with a history of esophageal surgery, fundoplication, more than one acid suppression medication or taking any acid suppression medications other than ranitidine or lansoprazole were excluded from the study.

Of these, 186 infants less than 12 months of age met the inclusion criteria and were initially divided in 3 groups: those on no acid suppression, those on ranitidine and those of lansoprazole. To evaluate feeding regimen we excluded 12 infants in which feeding information was missing and the remaining 174 infants were divided into 3 feeding groups: nasogastric (NG) tube,
gastrostomy tube (GT) and oral (PO). We further divided the NG group into those fed bolus and those fed continuously.

The infant catheter (Sandhill Scientific Inc, Highland Ranch, CO), with six impedance sensors (1.5 cm apart) and the pH sensor at the distal impedance recording site, was used for all the studies. By chest X-ray the most distal electrode was estimated to be 2 cm above the LES. Data were collected over a minimum of 18 hours and analyzed using the BioVIEW software (Sandhill Scientific). Space-time impedance variations were displayed as contour plots.

**Variable Definition**

Reflux events (indicated by a retrograde decrease in impedance baseline that exceeded 50% of the distance between the baseline and the impedance nadir in at least the 2 distal channels) were counted and characterized as acid (pH<4 for at least 5 seconds) or non-acid. Proximal reflux events were also counted (defined by a drop in impedance by at least 50% from baseline in either of the two most proximal impedance channels). In addition we also recorded the acid exposure time defined as the percentage of study time that the pH was <4. Pure gas reflux events were not included in the reflux analysis.

Symptom index (SI) was calculated as the percentage of symptoms that were reflux related, i.e., the percentage of symptom episodes that had a documented reflux episode within 5 minutes (2.5 minutes before and 2.5 minutes after the symptom). This was calculated as number of acid related symptoms/total number of symptoms x 100%. The cut-off value used for a positive SI was \( \geq 50\% \) according to previously published data \(^{10}\) and calculated by the Sandhill Scientific Inc. software. For each patient we also included the total number of symptom events and total
number of reflux events (total, acid and non acid) that were associated within 5 minutes of each symptom.

Statistical Analysis

Using univariate analysis the total number of reflux events, number of acid and non acid reflux events, number of proximal reflux events and acid exposure time, age, feeding regimen, and sex were compared for normality of the data. Then the appropriate comparison technique for the data was applied: Kruskal-Wallis Test with post hoc analysis utilizing the Dunn multiple comparison adjustment, ANOVA with Tukey correction for post hoc analysis and Chi Square for categorical data.

A multivariate logistic regression model was built with the independent variable being the presence or absence of a positive SI. Included in the model were: total number of acid reflux events, total number of nonacid reflux events, age, weight, number of proximal reflux events, sex, total number of symptoms, medications and feeding method. We utilized negative binomial distribution to analyze count data, analyzing the total related reflux events offsetting for the total number of symptoms. In this model we also included total number of acid and nonacid reflux events, age, weight, number of proximal reflux events, sex, medications and feeding method. When symptom frequency was low the model was adjusted by dropping variables found to be insignificant and noncontributory to the model. Chi square was used to compare the total number of acid and non acid reflux events to acid related symptoms and to non acid related symptoms.

Results

Of the 186 infants 117 (63%) were males and 69 (37%) females with a mean age (standard deviation) age of 5.4 ± 3.4 months. Of these, 92 infants were fed orally during the study and 94
received enteral feeds either via a NG or GT. The indications for pH-MII in our population are many, including frequent regurgitation/vomiting, suspected acute life threatening events (ALTEs), feeding disorder, respiratory symptoms, and patients evaluated for placement of G tubes.

Sixty-eight (68) received no acid suppression medications at least for 7 days before the study, 42 were on ranitidine and 76 on lansoprazole during the study. Infants in the ranitidine group were younger than the other groups (p=0.008) but there was no difference in gender or method of feeding among the three groups. (Table 1). The mean dose of lansoprazole was 1.75 mg/kg/day and the mean dose of ranitidine was 4.5 mg/kg/day.

There was no difference in the total number of reflux events or number of proximal reflux events between the medication groups. Infants receiving lansoprazole had significantly fewer number of acid reflux events (p<0.0001), but there was no difference in the number of acid reflux events between infants receiving ranitidine or those on no acid suppression medication. The lansoprazole group had decreased acid exposure time when compared to those on no medication (p=0.003) but it was not significant when compared to ranitidine (p=0.065).

In the reference group (on no acid suppressant medications), the median number and interquartile range (IQR) of total reflux events was 49.5 (23-73), with a median number of 13 (4.5-32) acid events, and a median acid exposure time of 0.65% (0 – 2.9%). At least three quarters of the infants in this group had normal acid exposure time and number of acid reflux events, based on previously published infant normal pH probe parameters\(^{11}\).

A total of 4159 symptoms were recorded during the studies; 1504 (36 %) were associated with a reflux event and only 369 (9%) were associated with an acid reflux event. When total number of reflux episodes and events are taken into consideration, acid reflux episodes are as likely to be
associated with a symptom as non acid events (p=0.66). This remained true when we analyzed each individual symptom (table 2).

Age, method of feeding, medications, number of proximal reflux events and sex were not associated with symptom correlation in both the categorical and count analysis. Only total number of acid and non acid reflux episodes were associated with a higher symptom correlation with an Odds Ratio (OR) of 1.034 (1.006-1.062) (p=0.016) and 1.027 (1.010-1.045) (p=0.002) respectively.

We evaluated the association between reflux and a number of specific symptoms (Table 2):

a) Cough: 164 infants were reported to cough during the study and 48 (29%) had a positive SI. Out of 3074 episodes of cough only 1037 (34%) were reflux related and 252 (8%) related to acid reflux. Age, proximal episodes, weight, sex, and medications had no relation to coughing related reflux events. Total number of acid and non acid reflux episodes were associated with a higher symptom correlation. Categorical analysis showed that in patients with positive SI for cough there were an increased number of non acid events (OR= 1.029, range 1.011-1.047) (p=0.001).

b) Regurgitation: 115 infants were reported to have regurgitation during the study and 58 (50%) had a positive SI. Out of 500 episodes of regurgitation 262 (52%) were associated with a reflux event with 74 (14%) related to acid reflux. Both categorical and count analyses showed a positive association of regurgitation with total number of reflux events. Patients with positive symptom correlation for regurgitation are more likely to have more acid (OR=1.053, range 1.015-1.093) (p=0.005) and nonacid (OR=1.029, range 1.004-1.054) (p=0.023) reflux events as well as tend to be younger OR 0.058 (p=0.04).
c) Gag: 48 infants were reported to gag during the study and 21 (44%) had a positive SI. Gagging was reported a total of 220 times; 78 (35%) were reflux related and 13 (6%) related to acid reflux. By count analysis none of the variables were found to be associated.

d) Desaturation: 17 infants were reported to have oxygen desaturations during the study; 3 (18%) had a positive SI. A total of 96 desaturations were reported and 18 (19%) were associated with a reflux event; 1(1%) was related to an acid reflux event. Count analysis showed a significant association of younger age and enteral feeds (OR=0.12, range 0.016-0.889) (p=0.038) with reflux associated episodes of desaturation. Number of reflux events or proximal extent of reflux events were not associated with risk of desaturation events.

e) Pain: To facilitate analysis we combined the following symptoms to be analyzed as “pain” (crying, restlessness, head side/side, thrashing, pain, screaming, and fussiness). Out of the 186 infants, 11 were reported to have episodes related to pain during the study and a total of 36 episodes were reported; 13 were associated with reflux events and none with acid reflux events. Negative binomial regression showed no association with age or number of acid and non acid reflux events.

The remainder of the symptoms did not have sufficient numbers to facilitate statistical evaluation. The number of episodes and related episodes are shown in Table 2.

Sixty nine patients were fed via NG tube during the study; 14 through GT and 91 by mouth. The NG fed group had less total reflux episodes when compared to the PO fed group (p=0.012) and
no difference was seen when compared to the GT fed group (p=0.64). There was no difference in use of acid suppression medications between the groups (p=0.51).

The NG tube fed group was significantly younger than the PO and GT fed group (p<0.0001). There was no significant difference in the number of proximal reflux events (p=0.125), number of acid reflux episodes (p=0.116) or acid exposure time(p=0.33) between the three groups. (Table 3). In the NG tube fed group there was no difference in age (p=0.21), the number of total (p=0.84), proximal (p=0.29) or acid (p=0.31) reflux events between those infants fed continuously and those fed by bolus (Table 4).

**Discussion**

Our study was designed to evaluate the effectiveness of acid suppression in infants and the association between reflux and symptoms. No difference was noted in the number of acid reflux events or acid exposure time between infants receiving ranitidine and those on no acid suppression medication. This could suggest that ranitidine was ineffective in reducing acid reflux at the dose used. However, we do not have data on the duration of ranitidine therapy and rather than lack of efficacy this finding could be explained by the development of tachyphylaxis which has been observed in adults.\(^{12}\) It is also likely that infants who reportedly improve on ranitidine do indeed respond initially but as its efficacy decreases the physiologic processes that naturally decreases reflux in infants with maturity takes over.

Lansoprazole was more effective than ranitidine in reducing esophageal acid exposure time and acid reflux events but did not decrease the total number of reflux events or the proximal extent of these reflux episodes. Therefore lansoprazole therapy may not decrease the number of ‘spit ups’ but would be expected to alleviate symptoms caused or aggravated by acid.
Non-acid reflux events are as likely as acid reflux events to be associated with symptoms. Although lansoprazole is more efficacious than either ranitidine or no medication therapy in decreasing acid exposure time and number of acid reflux events, acid suppression did not result in change in symptoms in infants tested. The greater the total number of reflux events the more likely they are to be associated with any symptom. Although for some conditions the OR reaches statistical significance, in general the OR is so close to 1 that it has no clinical significance. In most cases there is not an association with symptoms and acid reflux. Although we can’t establish causality based on this data, we can infer that most of the caregiver reported symptoms are erroneously perceived to be caused by GER and acid-related reflux.

Regurgitation had one of the highest symptom/reflux correlations. Also as expected, younger age was strongly associated with the correlation of regurgitation, since it has been proven that regurgitation resolves with age.\(^6\)

GER is likely not to be the cause of coughing. In spite of being the most frequent symptom it had very low symptom correlation. Only 34% of the coughing events were temporally associated with a reflux event. This doesn’t prove causality because increased intra-abdominal pressure when coughing could still cause a reflux episode. Based on this data we would not anticipate acid suppression medications to have an effect on coughing. We suggest that other causes of coughing should be evaluated before treating for GERD. If this initial work up is negative and one still suspects GERD a Ph-MII probe may be indicated. In our model, coughing was associated with a higher number of reflux events but the OR is of no clinical significance.

Pain (which included crying, restlessness, thrashing, fussiness, pain, head side/side) and gagging had no association with any GER characteristics. Back arching was analyzed separately (Table 2) because of the large implied association with GERD. Interestingly, 55% of back arching
episodes were associated with reflux events but none of them were acid, demonstrating that not all back arching is related to reflux and that nonacid events can cause the same symptoms as acid events. Most of the symptoms perceived by the caregivers as pain are not associated with a reflux event, but when any of these or back arching is associated with a reflux event it is unclear if this is due to visceral hyperalgesia in response to the sensation of the refluxate in the esophagus. pH-impedance does not measure volume of the reflux. It could be that the higher the volume of the refluxate the more likely it is to cause discomfort or a vagal response and not necessarily pain. It is also possible that these events are temporally related but not causal.

When we analyzed the infants that had desaturation episodes during the study, our analyses showed that desaturation events were not associated with the number of or characteristics of the reflux events. Younger age was significantly associated with desaturations as would be expected since younger infants are more likely to have desaturation events than older infants. We were surprised to find that enteral feeds (whether NG or GT) were negatively associated with reflux related desaturation episodes. This could be because young infants receiving oral feeds might have an immature swallow mechanism or because PO fed infants have higher number of reflux events than those on NG or GT feeds making a temporal association more likely without causality. Whether NG feeds are associated with an increase in the number of reflux events or aggravate reflux events has been debated. We found that NG feeds, whether continuous or bolus, did not increase GER episodes but that actually orally fed infants have a higher number of reflux events. This might be because orally fed infants swallow more air with a subsequent increase in gastric pressure resulting in an increase number of reflux events. It is important to remember that we have no data on the volume of feeding and these results could also be explained if the NG group had less volume per weight. We did not find a difference between GT
and NG fed infants, suggesting that tolerating NG feeds is an adequate screen for tolerance of GT feeds.

There are potential risks associated with the use of PPIs including side effects that have been reported to occur in up to 14% of children, and there is increasing evidence that acid suppression by H2RBs and PPIs may increase rates of community acquired pneumonia and gastroenteritis in children and candidemia and necrotizing enterocolitis in preterm infants. The recent NASPGHAN guidelines state that there is no evidence to support empiric trial of pharmacologic treatment in infants with symptoms suggestive of GERD. At least three quarters of the infants in our study were on no acid suppression and had normal acid exposure time of 2.9% compared with normal published data of <10% and normal number of acid reflux events. Our findings that nonacid reflux episodes are as likely to be associated with symptoms as acid events reinforces the wisdom of this approach and further supports abandoning the empirical trial of acid suppression algorithm.

This study is based on retrospective chart review and therefore susceptible to all the limitations and biases. During the impedance study caregivers might not have pressed the symptom button every time a symptom was present, (especially during the night) or might have pressed the symptom button after the allotted 2.5 minute margin. Some of the strengths of our study include the large number of infants and that pH-impedance is the most objective method of evaluating acid and non-acid reflux events as well as symptom correlation.

Symptoms Most of the attributable of GERD in infants such as cough, gagging, pain and desaturation are less likely to be associated with a reflux event and have very poor symptom correlation to reflux. In those patients for which an association exists, non-acid episodes are as likely to cause symptoms as acid reflux episodes. If the symptoms are still suspected to be due to
GERD, a combined pH-impedance study may be indicated before putting the infant on long-term acid suppression therapy. Risk benefits of treatment should be weighed and appropriate expectations should be discussed with families.
References

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>No Medication</th>
<th>Ranitidine</th>
<th>Lansoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>68</td>
<td>42</td>
<td>76</td>
</tr>
<tr>
<td>Mean Age (months)</td>
<td>0.48</td>
<td>0.33*</td>
<td>0.49</td>
</tr>
<tr>
<td>Male</td>
<td>42 (62%)</td>
<td>27 (64%)</td>
<td>48 (63%)</td>
</tr>
<tr>
<td>Feeding regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO</td>
<td>37 (54%)</td>
<td>20 (48%)</td>
<td>35 (46%)</td>
</tr>
<tr>
<td>Enteral</td>
<td>31 (46%)</td>
<td>22 (52%)</td>
<td>41 (54%)</td>
</tr>
<tr>
<td>Median Total Reflux Events (IQR)</td>
<td>49.5 (23.5-73.5)</td>
<td>54.5 (37-81)</td>
<td>54 (26-85)</td>
</tr>
<tr>
<td>Median Acid Reflux Events (IQR)</td>
<td>13 (4.5-32.5)</td>
<td>13 (3-22)</td>
<td>4* (0-10)</td>
</tr>
<tr>
<td>Median Proximal Reflux Events (IQR)</td>
<td>15.5 (1-44)</td>
<td>21 (4-41)</td>
<td>11.5 (5-35)</td>
</tr>
<tr>
<td>Median % Acid Exposure time (IQR)</td>
<td>0.65 (0-2.9)</td>
<td>0.35 (0-2.2)</td>
<td>0.1^ (0-0.8)</td>
</tr>
</tbody>
</table>

IQR= Inter quartile range; *significantly different from both groups; ^significantly different from no medication group
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of infants with symptom</th>
<th>Number of infants with positive SI</th>
<th>Number of infants with negative SI</th>
<th>Total number of symptoms</th>
<th>Total number related to reflux</th>
<th>Total number related to Acid reflux</th>
<th>X² p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>164</td>
<td>48 (29%)</td>
<td>116 (71%)</td>
<td>3074</td>
<td>1037 (34%)</td>
<td>252 (8%)</td>
<td>p=0.65</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>115</td>
<td>58 (50%)</td>
<td>57 (50%)</td>
<td>500</td>
<td>262 (52%)</td>
<td>74 (14%)</td>
<td>p=0.62</td>
</tr>
<tr>
<td>Gag</td>
<td>48</td>
<td>21 (44%)</td>
<td>27 (56%)</td>
<td>220</td>
<td>78 (35%)</td>
<td>13 (6%)</td>
<td>p=0.14</td>
</tr>
<tr>
<td>Desaturation</td>
<td>17</td>
<td>3 (18%)</td>
<td>14 (82%)</td>
<td>96</td>
<td>18 (19%)</td>
<td>1 (1%)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Belch</td>
<td>11</td>
<td>7 (64%)</td>
<td>4 (36%)</td>
<td>73</td>
<td>48 (66%)</td>
<td>20 (34%)</td>
<td>p=0.15</td>
</tr>
<tr>
<td>Pain</td>
<td>11</td>
<td>4 (36%)</td>
<td>7 (64%)</td>
<td>36</td>
<td>13 (36%)</td>
<td>0</td>
<td>p=0.38</td>
</tr>
<tr>
<td>Retching</td>
<td>7</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td>37</td>
<td>17 (46%)</td>
<td>2 (5%)</td>
<td>p=0.74</td>
</tr>
<tr>
<td>Back Arching</td>
<td>9</td>
<td>5 (55%)</td>
<td>4 (45%)</td>
<td>24</td>
<td>10 (42%)</td>
<td>0</td>
<td>p=0.128</td>
</tr>
<tr>
<td>Sneeze</td>
<td>7</td>
<td>2 (28%)</td>
<td>5 (72%)</td>
<td>25</td>
<td>6 (24%)</td>
<td>2 (8%)</td>
<td>p=0.25</td>
</tr>
<tr>
<td>Hiccup</td>
<td>6</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>8</td>
<td>4 (50%)</td>
<td>1 (12%)</td>
<td>p=0.49</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3</td>
<td>0</td>
<td>3 (100%)</td>
<td>17</td>
<td>1 (6%)</td>
<td>0</td>
<td>0.28</td>
</tr>
<tr>
<td>Other Respiratory</td>
<td>9</td>
<td>3 (33.3%)</td>
<td>6 (66.6%)</td>
<td>31</td>
<td>9 (29%)</td>
<td>3 (10%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Other respiratory includes= (wheezing, stridor, gasping, gurgle, grunting)
Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Gastrostomy tube n=14</th>
<th>Nasogastric tube n= 69</th>
<th>Oral n= 91</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (months)</td>
<td>0.54 ± 0.26</td>
<td><em><em>0.33</em> ± 0.23</em>*</td>
<td>0.52 ± 0.28</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Males</td>
<td>8 (57%)</td>
<td>39 (56.7%)</td>
<td>60 (66%)</td>
<td>p=0.451</td>
</tr>
<tr>
<td>Median number of Total Reflux Events (IQR)</td>
<td>41 (21-74)</td>
<td>44 (24-74)</td>
<td>*<em>62</em> (37-86)</td>
<td><strong>p=0.022</strong></td>
</tr>
<tr>
<td>Median number of Acid Reflux Events (IQR)</td>
<td>11 (0-33)</td>
<td>7(1-20)</td>
<td>11 (4-25)</td>
<td>p=0.116</td>
</tr>
<tr>
<td>Median number of Proximal Reflux Events (IQR)</td>
<td>10 (1-22)</td>
<td>12 (2-35)</td>
<td>20 (6-51)</td>
<td>p=0.125</td>
</tr>
<tr>
<td>Median % Acid Exposure time (IQR)</td>
<td>0 (0-1.6)</td>
<td>0.1 (0-2)</td>
<td>0.4 (0-1.8)</td>
<td>p=0.33</td>
</tr>
</tbody>
</table>

IQR= Inter quartile range; *significantly different from both groups
Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Bolus Feeds</th>
<th>Continuous Feeds</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Mean Age (months)</td>
<td>0.3 ± 0.23</td>
<td>0.38 ± 0.22</td>
</tr>
<tr>
<td>Median number of Total Reflux Events (IQR)</td>
<td>50 (25-72)</td>
<td>43 (19-81)</td>
</tr>
<tr>
<td>Median number of Acid Reflux Events (IQR)</td>
<td>4 (1-16)</td>
<td>10 (1.5-21)</td>
</tr>
<tr>
<td>Median number of Proximal Reflux Events (IQR)</td>
<td>12 (0-33)</td>
<td>16 (5.5-48.5)</td>
</tr>
</tbody>
</table>