The Management of Gastro-oesophageal Reflux in Infants

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ABSTRACT

Objective: To determine the optimal management of gastro-oesophageal reflux in infants. **Methods**: Searches were made on medical databases (Cochrane Library, National Electronic Library for Health, PubMed). Three randomised control studies, a case control study, an intervention study and one systematic review were chosen and appraised according to a critical appraisal checklist. **Results**: Antacids and feed thickeners were found to be effective in decreasing the symptoms, but not the gastric acidity associated with gastro-oesophageal reflux. There was no evidence supporting the use of positioning in decreasing symptoms. No evidence was found to support the use of pharmacological agents (metoclopramide, omeprazole) in the treatment of gastro-oesophageal reflux. **Conclusion**: The optimal management of gastro-oesophageal reflux in infants is parental reassurance and education. If essential, conservative measures such as feed thickeners and antacids may be employed.

INTRODUCTION

Gastro-oesophageal reflux (GOR) is a common self-limiting condition, affecting up to two thirds of infants, that usually resolves by six to 12 months of age (Figure 1).[1] It is usually a normal physiological process involving regurgitation and is described by the lay public as "spitting up". This type of emesis is effortless where there is passive return of gastric contents into the oesophagus, and occurs by three major mechanisms: transient lower oesophageal sphincter relaxation, increased intra-abdominal pressure (for example, sneezing, coughing), or spontaneous free reflux.

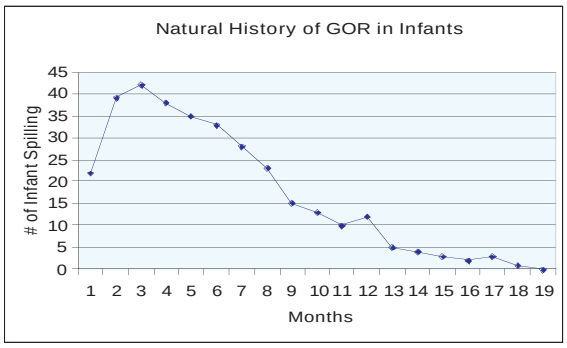

Figure 1. *Natural History of Gastro-Oesophageal Reflux (adapted from Martin et al, 2002).*

Gastro-oesophageal reflux disease (GORD) on the other hand, which affects only 1 in 300 infants, is a pathological process manifested by poor weight gain, persistent respiratory symptoms and signs of oesophagitis (Table 1).[2]

Patients with mild, uncomplicated reflux can be diagnosed clinically and treated without further investigations. The typical clinical features include post-prandial, persistent but effortless non-bilious emesis, and regurgitation with normal weight gain.

GORD	**GOR**
Regurgitation with **poor weight gain**	Regurgitation with **normal weight gain**
Apnoea & Cyanosis Wheezing Recurrent pneumonia Chronic cough Stridor	No significant respiratory symptoms
Irritability Haematemesis Iron deficiency anaemia Failure to thrive	No signs or symptoms of oesophagitis
Neck tilting (Sandifer's syndrome)	No neurobehavioural symptoms

Table 1. *Differences between Gastro-Oesophageal Reflux (GOR) and Gastro-Oesophageal Reflux Disease (GORD) (adapted from Jung, 2001).*

A good history and clinical examination will usually distinguish between GOR and other conditions with similar presentations, such as pyloric stenosis. The 24-hour pH study is considered the "gold standard" for confirming or excluding the presence of abnormal GOR. The reflux index, which is the percentage of total time that oesophageal pH is less than 4.0, provides the most efficient interpretation of the test, with a sensitivity of 96 percent, specificity of 100 percent.[3] Additional parameters that can be measured include number of reflux episodes, number of reflux episodes lasting more than five minutes, the mean duration of each reflux episode, and the duration of the longest reflux episode, within the 24-hour period.

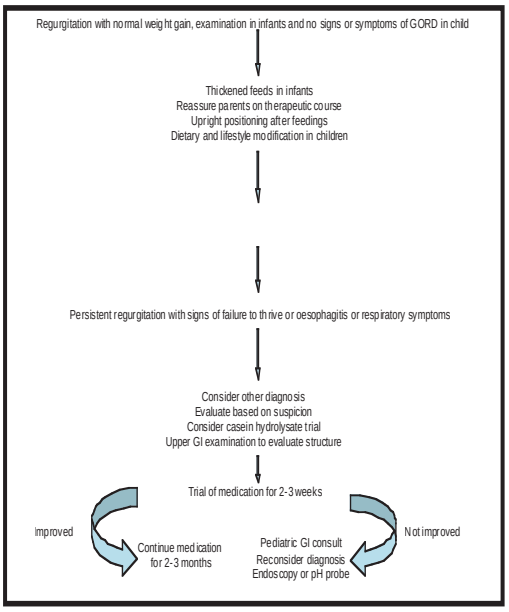

Figure 2. *The American Family of Physicians' Proposed Management in Infants Presenting with Gastro-Oesophageal Reflux and Gastro-Oesophageal Reflux Disease (adapted from Jung, 2001).*

The American Family of Physicians (Figure 2) recommends that parental reassurance and education about the widespread prevalence of physiologic (functional) GOR in infants, especially among those one to four month old, is the most effective management.[2] Other conservative measures recommended include thickening of feeds, dietary changes, and positional changes (the prone position may decrease the incidence of reflux as demonstrated in Figure 3).[4] If the infant does not improve and shows signs of failure to thrive, then various pharmacological interventions are recommended, and these include antacids, H_2 receptor antagonists, proton pump inhibitors and prokinetic agents.

The aim of our study was to determine the optimal

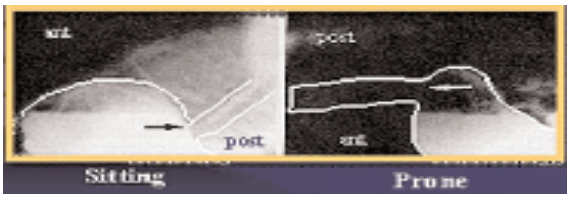

Figure 3. *Barium Study of Infants in the Sitting and Prone Positions, Indicating the Reduced Likelihood of Gastro-Oesophageal Reflux Occurring in the Sitting Position. (adapted from Bishop, 2004).*

management of gastro-oesophageal reflux in infants, through a systematic review of recent studies.

METHODS

Medical databases, such as the Cochrane Library, the National Electronic Library for Health and PubMed were searched for relevant articles using the following keywords: GER, GOR, gastro-oesophageal reflux, infant, treatment, drug names such as antacid, metoclopramide, H_2–receptor antagonist and proton pump inhibitor. Of all articles found, the six most relevant to the clinical question were chosen. They included three randomised control studies (RCT), a case control study, an intervention study and one systematic review. They were then appraised according to a critical appraisal checklist.[5] (Tables 2, 3 and 4)

a. Criteria for SR clearly stated?	√
b. Literature review extensive enough?	√
c. Was quality of studies assessed?	√
d. Results of assessment included?	X
e. Details of studies included in SR?	√
f. Results of individual studies pooled correctly?	Not reported
g. Meta-analysis done?	Not reported
h. Do SR findings add up to more than a sum of individual studies?	X

Table 2. *Appraisal Methodology Checklist for the Systematic Review (SR).*

	Article 1	Article 2	Article 3
Essential Questions			
• All patients accounted for?	√	√	√
• Outcomes assessed blind?	√	√	√
Design			
- Aims clearly stated?	√	√	√
- Measurements valid & reliable?	√	√	√
- Outcomes clinically relevant?	√	√	√
Analysis			
– Treatment groups comparable at baseline	√	√	√
– Were there deviations from planned treatment?	X	X	X
– Results analyzed by Intention to treat?	√	√	√
– Stat. significance assessed?	√	√	√
– Side effects?	√	X	X

Table 3. *Appraisal Methodology Checklist for the Three Randomized Control Trials (RCT).*

	Article 4	Article 5
Essential Questions		
- How were cases obtained?	After diagnosis at research hospital	Referred to research hospital
- Data collected in same way?	√- Questionnaire	√
Design		
• Aims clearly stated?	√	√
• Measurements valid & reliable?	√	√
Analysis		
• Statistical significance assessed?	√	√
Interpretation		
– Biases?	X	Recall, measurement bias
– Confounding variables	Socioeconomic class	X

Table 4. *Appraisal Methodology Checklist for the Article 4 (the Case Control Study) and Article 5 (the Intervention Study).*

RESULTS

The first article under review was a double-blinded RCT assessing the efficacy and safety of aluminium-free alginate versus placebo in 90 infants with recurrent GOR.[6] Infants were assessed at baeline and at seven and 14 days after initiation of treatment. Among 42 patients randomised to receive alginate and 48 patients to receive placebo, alginate was shown to be superior to placebo in reducing the number of reported vomiting or regurgitation episodes (p=0.09) (Figure 4). Although, treatment with placebo was also shown to reduce episodes, this effect did not achieve statistical signifcance. A trend in favour of alginate was also shown to reduce severity of vomiting (p=0.061). The main criticism of this trial was that there was potential for observer bias, since the number of episodes of emesis were subjectively assessed by the parents on a diary card. It was nevertheless concluded that the treatment outcome after active alginate therapy in infants with GOR, was considered superior to placebo by both the investigators and parents.

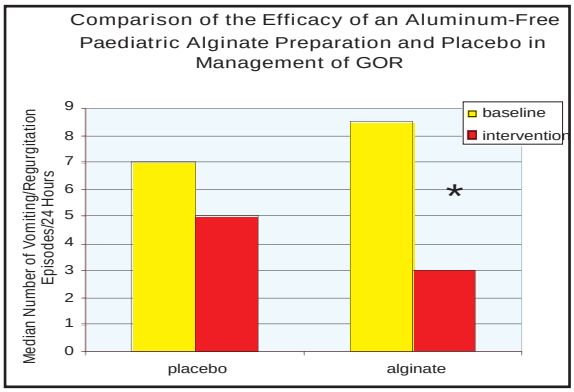

Figure 4. *Comparison of the Efficacy of an Aluminum-Free Paediatric Alginate Preparation and Placebo in the Management of Gastro-Oesophageal Reflux in Infants.*

The second article under review was a randomised, prospective double-blinded crossover trial investigating the efficacy of metoclopramide versus placebo in 30 infants[7]. Several parameters were measured including the average daily occurrence of symptoms and the percentage of time that oesophageal pH was less than 4.0 (the Reflux Index), the total number of episodes in a 24-hour period, and the total number of reflux episodes lasting more than five minutes in each 24-hour period. The results show that metoclopramide produced a decrease in the reflux index (p<0.001) (Figure 5). However, a significant placebo response (p<0.05) was also shown with respect to daily symptom scores.

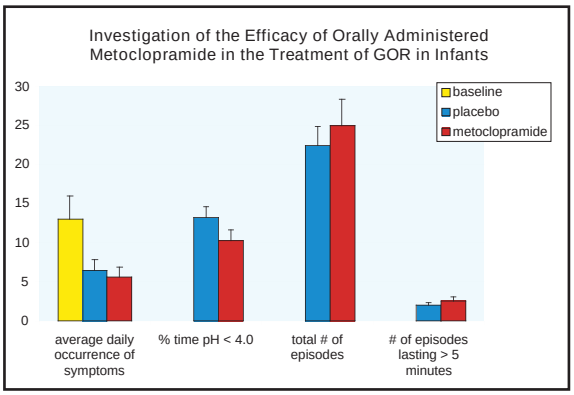

Figure 5. *Investigation of the Efficacy of Orally Administered Metoclopramide in the Treatment of Gastro-Oesophageal Reflux in Infants*

The main criticisms with this study were that even though it stated that the sample size of 30 was justified, there was no description of how that number was arrived at. In addition, the randomization procedures were not described. Even though this was a crossover design, there was no washout period between switching of the

groups; hence there may have been some overlap between the effects of metoclopramide in the two groups. However the investigators concluded that there was no difference between the two treatment groups in any of the parameters except the reflux index.

The third article was a double-blinded RCT assessing the efficacy of omeprazole in 30 irritable infants with GOR.[8] Parameters that were assessed included the reflux index, a cry/fuss diary and a visual analogue scale of infant irritability, as judged by parental impression; these latter two measures were obtained at baseline and at the end of each two-week treatment period. Omeprazole treatment was shown to significantly lower reflux index in comparison with placebo (-8.9 percent +/- 5.6 percent versus -1.9 percent +/- 2.0 percent, p<0.001) (Figure 6). No significant difference was shown in either the cry/fuss time or visual analogue measures. There was potential for observer bias in this study, since the cry/fuss diary and the visual analogue scale of infant irritability were subjectively judged by parental impression. However, it was concluded that compared with placebo, omeprazole significantly reduced oesophageal acid exposure but not infant irritability. Infant irritability improved with time, regardless of treatment.

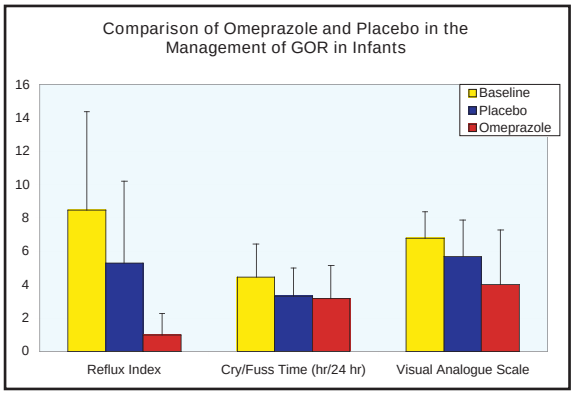

Figure 6. *Comparison of Omeprazole and Placebo in the Management of Gastro-Oesophageal Reflux in Infants.*

The fourth article was a case-control study comparing pre-thickened and home-thickened formulas in 100 infants with GOR.[9] Over a period of three months, infants were randomly selected to receive conventional formula with starch or pre-thickened infant formula. The investigators measured the effect of both pre-thickened and hone-thickened formula and the frequency of regurgitation mad vomiting. the progression of the patients' symptoms were classified as cured, if initial symptoms disappeared or improved, when frequency of symptoms were reduced by 50 percent or greater. Both types of thickened formula relieved reflux. Approximately half of the pre-thickened group and two-fifths of the home-thickened group achieved cure. The small differenc in cure rates observed between groups was not significant (p=0.297). Similarly only a small difference in rates of improvement was found between groups(p=1.00) (Figure 7.). Also, the study was not blinded and the results were collected via a subjective questionnaire.

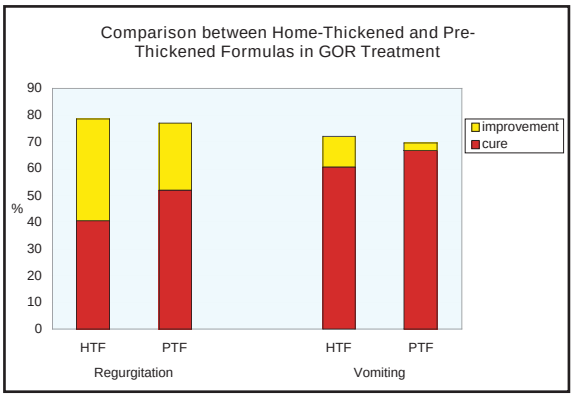

Figure 7. *Comparison between Home-Thickened and Pre-Thickened Formulas in the Treatment of Gastro-Oesophageal Reflux in Infants.*

The fifth article was a prospective intervention study evaluating the effect of smaller volume, thickened formulas on GOR in 12 thriving infants.[10] Two parameters were measured, the number of emesis episodes in each 24-hour period and the reflux index. The study showed reduced vloume of formula decreased the frequency of emesis but not by a significant margin (p>0.05). However, additional modifications by thickening the small-volume feed, further decreased the frequency of emesis to a significant value compared to baseline (p<0.05) (Figure 8). The sample size was justified and the results were consistent with previous reports, however this study was not randomised or blinded, thus introducing the potential for recall and measurement bias. In addition, the trial protocol required feeds that were strictly controlled, which was not applicable to the general population.

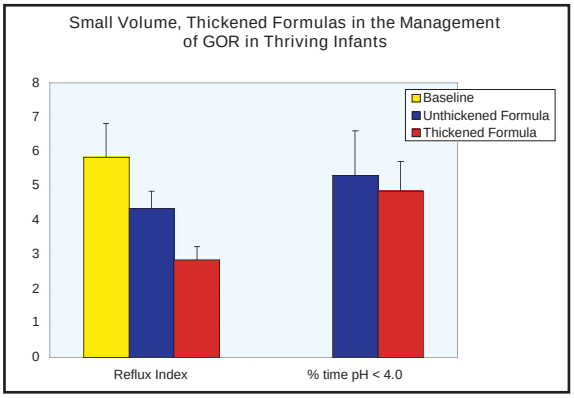

Figure 8. *Small Volume, Thickened Formulas in the Management of Gastro-Oesophageal Reflux in Thriving Infants.*

The sixth article was a systematic review of non-pharmacological and non-surgical therapies in 323 infants with GOR.[11] It examined three main aspects of conservative treatment: positioning, thickened feeds and formula changes. In terms of positioning, three RCTs found that positional changes have no proven efficacy in the treatment of GOR. With regard to thickened feeds, four randomized controlled trials indicated that there was a significant reduction in emesis with thickened feeds vs. unthickened feeds, however no significant difference was found in the amount of reflux. With formula changes, two RCTs showed that whey-based formulas significantly decreased emesis but had no effect on oesophageal pH (Table 5).

While inclusion criteria for this systematic review were provided, the outcome criteria were not. Other limitations of the study were a language and publication bias, since only English articles were considered. The outcomes were not comparable between the various studies as there was no description of a formal statistical method for assessing differences between the studies.

Management	Result
Feed thickeners	↓ emesis
Positioning changes	No effect
Formula change	↓ emesis but no effect on oesophgeal pH
Antacids (alginate)	↓ number & severity of vomiting episodes
Pro-Kinetic agents (metoclopromide)	No ↓ in daily symptoms or number of episodes but _ in time oesophageal pH <4.0
Proton Pump Inhibitors (omeprazole)	↓ oesophageal acid exposure but not irritability
H_2 Receptor Antagonists	No studies found for use in infants

Table 5. *Summary of the Results in the Management of Infants with Gastro-Oesophageal Reflux.*

DISCUSSION

Following the review of current literature on the treatment of gastro-oesophageal reflux, it was determined that the best line of treatment involves parental reassurance and education. No evidence was found to support the use of pharmacological agents in the treatment of GOR. Although both pro-kinetic agents and proton pump inhibitors may reduce oesophageal acid exposure, they do not have any effect on the symptoms of GOR, including infant irritability; which will improve with time, regardless of treatment. In contrast, this review found that antacids and feed thickeners were most effective in decreasing the symptoms, but not gastric acidity associated with GOR. There was no evidence supporting the use of positioning in decreasing the symptoms.

When a parent presents to a doctor with an infant that vomits after every feed, he/she will find it difficult to accept that regurgitation is a normal occurrence. Providing parents with education surrounding this common and normal physiological process is essential to reducing their anxiety and concern. However, if an infant shows features of failure to thrive with persistent respiratory symptoms and signs of oesophagitis, which are manifestations of GORD affecting only 1 in 300 infants, then this would require admission and further evaluation.

Gastro-oesophageal reflux is a self-limiting condition that usually resolves by six to 12 months of age. Infant irritability tends to improve with time, which could be a confounding factor in any study involving therapeutic intervention of GOR. Reassurance and parent education is paramount and should be the first-line of management. If parents insist, conservative treatment may be employed.

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