Investigation and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units

Thomas Rossor[1], Gwendolyn Andradi[1], Ravindra Bhat[2], Anne Greenough[1,3]

[1]Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London; [2]Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London; [3]NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

Short title: Investigation and management of GOR

Address for correspondence: Professor Anne Greenough, Neonatal Intensive Care Unit, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom. Tel: 0203 299 3037; fax: 0203 299 8284

Email: anne.greenough@kcl.ac.uk

ABSTRACT

Aim: In 2004 wide variation in the investigation and management of gastro-oesophageal reflux (GOR) of infants on UK major neonatal units was demonstrated. Our aim was to re-survey neonatal practitioners to determine current practice and whether it was now evidence based.

Methods: A questionnaire was sent to all 207 UK neonatal units.

Results: Responses were obtained from 84% of units. The most frequent "investigation" was a trial of therapy (83% of units); pH studies were used in 38%, upper GI contrast studies in 19% and multichannel intraluminal impedance (MII)/pH studies in 5%. Only six units suggested a threshold for an abnormal pH study and two units for an abnormal MII study. Infants were commenced on anti-reflux medication without investigation always in 32% of units, often in 29%, occasionally in 19% and only never in 1%. Gaviscon was used as first line treatment in 60% of units, other medications included ranitidine in 53%, thickening agents in 27%, proton pump inhibitors in 23%, domperidone in 22% and erythromycin in 6%.

Conclusion: There remains a wide variation in diagnostic and treatment strategies for infants with suspected GOR on neonatal intensive care units, emphasizing the need for randomised trials to determine appropriate GOR management.

Key words: gastro-oesophageal reflux; multichannel intraluminal impedance (MII) study; pH study.

List of abbreviations

GOR – gastro-oesophageal reflux

GORD - gastro-oesophageal reflux disease

MII - multichannel intraluminal impedance

NEC – necrotising enterocolitis

KEY NOTES

- Many infants on neonatal units receive treatment for suspected gastro-oesophageal reflux (GOR).
- We have demonstrated a wide variation in the investigation and management strategies of suspected GOR on neonatal units.
- There is a need for randomised trials to identify appropriate diagnostic and intervention strategies in neonates with suspected GOR.

INTRODUCTION

Gastro-oesophageal reflux (GOR), the retrograde movement of gastric contents into the oesophagus, is a common event even in healthy infants (1). Gastro-oesophageal reflux disease (GORD) occurs when the reflux causes troublesome symptoms. The symptoms attributed to GORD, however, are varied and non-specific and include that the infant is unsettled, has poor weight gain, back arching, poor feeding and/or respiratory disturbance, including apnoea. Many infants on neonatal intensive care units (NICUs) are treated for GORD, for example approximately 25% of 1598 extremely low birth weight (<1000g) infants were discharged from NICUs in the USA on anti-reflux medication (2). In 2004, a survey was reported of the diagnostic and treatment strategies for GORD in major NICUs in the United Kingdom (3). A wide variation in strategies was demonstrated, which the authors postulated resulted from the lack of published evidence (3). The aim of this study was to conduct a further survey more than a decade later to determine current diagnostic and treatment strategies and if practice now reflected whether there was an increased evidence base.

METHODS

A questionnaire was sent to clinicians of all 207 UK neonatal units identified from the National Neonatal Audit Programme, the British Association of Perinatal Medicine directory and a departmental database established for previous audits. Practitioners were asked which investigations were used, what thresholds were considered abnormal for pH and multichannel intraluminal impendence (MII) studies and what proportion of infants were investigated prior to initiation of therapy for GORD. In addition, they were asked which medications were used and what criteria were used for discontinuing treatment. The survey included all infants cared for on a neonatal unit, that is those born prematurely or at term.

RESULTS

Responses were obtained from 84% of the 207 UK neonatal units. To establish the diagnosis, the majority (58%) of units used a trial of treatment; investigations were used less frequently (Table 1) Only six units suggested a threshold for an abnormal pH study. An acid index of more than 5% was considered abnormal in one unit, more than 7% in two units and more than 10% in three units. Only two units gave a threshold for an abnormal MII study and in both this was more than 50 reflux events in 24 hours. In only two units (1%) was anti-reflux medication never started prior to investigation and in 32% of units medication was always started without investigation. In a further 29% of units treatment was often started without investigation and in another 19% of units occasionally without investigation.

The type of treatment used varied widely between neonatal units (Table 2). Therapy was discontinued in 44% units when symptoms resolved, in 9% of units prior to discharge and in 19% of units at the first out-patient appointment. Three percent of units undertook a trial of withdrawing treatment and medication was discontinued if there was no clear benefit.

DISCUSSION

We had demonstrated that there was a wide variation in the current investigation and management strategies for infants with suspected GORD being cared for on UK neonatal units. The previous survey (3) also showed a similar wide variation, but was only of prematurely born infants cared for in level two and three neonatal units. In our survey, all 207 neonatal units of all levels were surveyed with an 84% response rate. In addition, we asked about practice for all infants, regardless of maturity at birth.

A trial of therapy was the most commonly used approach to diagnose GORD and few neonatal units had access to pH or MII studies. Yet, although the latest guidelines from ESPGHAN conclude there is little evidence for any investigation of GORD in infants including neonates, they state that if there is a strong suspicion that reflux is contributing to apnoea combined pH/MII and polysomnography would be helpful. Indeed, addition of MII monitoring to conventional pH monitoring improved the diagnostic yield in 16 symptomatic preterm infants and seven neonates with apnoea (4). In contrast, in 54 infants with ages from 1-330 days, the prevalence of GOR as detected by MII-pH was low (10%), despite the infants having a strong clinical suspicion for reflux (5). In addition, in another study the majority of suspected clinical reflux behaviours did not correlate with reflux events (6).

In the 2004 survey, 30% of units used pH monitoring on a regular basis (3). The current survey revealed that still only a minority of units (34%) were using pH monitoring, perhaps reflecting the poor correlation between symptoms and the results of investigations (7) and/or the problems with interpreting the results. Reflex events are diagnosed if there is a reduction in the oesophageal pH below four. In infants, it has been suggested that such criteria may be of limited use as the gastric contents can be buffered by milk (8). The concerns regarding the buffering effect of milk, however, were based on data from studies with small numbers of heterogeneous groups of patients (9, 10). Other studies have shown that gastric pH dispersion is not homogeneous and have failed to find a significant effect of gastric buffering on the reflux index (11, 12).

In one study, although no statistically significant correlation was found between the pH reflux index and the duration of treatment, a significant correlation was demonstrated between MII results and the duration of treatment, but the correlation was weak (r^2=0.36) (13). In another study, amongst 64 infants with GOR symptoms who underwent MII/pH monitoring in the first

weeks after birth and then sequentially over the next three years, impedance bolus exposure index and proximal reflux frequency were most predictive of the duration of symptoms (5). Yet, we found only 5% of units used this technique. Only two units gave a threshold for an abnormal MII study, both used more than 50 events in 24 hours, whereas the recommended standard is 100 events in 24 hours. Upper GI contrast studies were used in 23% of units to diagnose GORD and, although they have a role in investigating anatomical abnormalities, they cannot quantify the frequency of reflux events and hence determine the severity (14, 15).

We have demonstrated that there remains a wide variety of medications used for GORD. Gaviscon was the most commonly used treatment, perhaps reflecting it has minimal side-effects (16). Gaviscon, however, is contraindicated in those with known or suspected impairment of renal function and should not be given with other preparations that contain thickening agents. Gaviscon is an alginate-based formulation and acts as a physical protection of the gastric mucosa. In the presence of gastric acid, sodium alginate precipitates to form a low-density but viscous gel. The sodium bicarbonate, usually contained in such formulations, is converted to carbon dioxide and is entrapped within the gel, forming a foam which floats on the surface of gastric content, preferentially moving into the esophagus instead of acidic gastric contents during GOR episodes. Gaviscon®, however did not reduce the frequency of GOR related apnoeas in 28 preterm infants studied with a six hour recording of combined MII and pH monitoring and polysomnography (17).

Other medications included histamine two receptor blockers, such as ranitidine and proton pump inhibitors, for example omeprazole have been shown to be efficacious in reducing gastric acid secretions and increasing gastric pH. Omeprazole administered at a daily dose of 0.7 mg/kg to preterm infants with suspected GORD reduced acid GOR frequency and the overall degree of esophageal acid exposure (18). In a double-blind placebo-controlled trial

of infants aged 3 to 12 months with GOR and/or oesophagitis, omeprazole compared to placebo significantly reduces oesophageal acid exposure, but not irritability (19). In contrast, Omari et al (20) demonstrated esomoprazole resulted in a significant decrease in the number of acid bolus reflux episodes and GORD related symptoms (20). Both proton pump inhibitors and histamine two (H_2) receptor blockers, however, have been associated with increased rates of necrotising enterocolitis (NEC) and serious bacterial infections (21). A systematic review, which included one case controlled and one prospective cohort study demonstrated a significant association between NEC and inhibitors of gastric acid production, as well as a higher incidence of infection (sepsis and pneumonia) (22). In a subsequent review, which included two retrospective and one prospective study, none of which were randomised, a significant association between use of ranitidine and an increased incidence of NEC was reported (23). Furthermore, 12 of 33 VLBW neonates who received H_2 antagonists developed blood stream infections, compared to 30 of 343 who did not receive the antagonist (24). A possible explanation is that the reduced gastric acid production might result in enhanced bacterial survival and gut colonization, increasing the risk of NEC development.

Dopamine receptor antagonists, such as the macrolides domperidone and erythromycin, have been reported to improve clinical symptoms, pH study indices and histological changes on oesophageal biopsy in older children with GORD compared to placebo. A systematic review evaluating the use of domperidone in the treatment of GORD in infants (25), however, concluded that there was insufficient evidence to support their use. Domperidone can precipitate cardiac arrhythmias (26), yet this survey showed it was currently used in 22% of UK neonatal units. Erythromycin use has been associated with hypertrophic pyloric stenosis (27), but was currently used for GORD in 6% of units.

Thickening agents were currently used in 27% of units. A new preterm formula thickened with amylopectin used in 28 symptomatic preterm newborns was shown to reduce the number of acid GOR episodes detected by pH monitoring, but not non acid GORs as detected by MII monitoring (28). Similarly, a study of 24 prematurely born infants demonstrated thickening a formula with amylopectin did reduce acid GOR, but not non acid GOR indexes nor GOR related apnoeas (29). A survey of neonatal feeding therapists and providers demonstrated that the majority were using thickened feeds for dysphagia or GORD, but noted variability in prescriptions for thickening agents regarding consistencies, thickening agents and recipes (30).

In conclusion, we have demonstrated there is wide variation regarding investigation and medication use in infants with suspected GORD in neonatal units in the UK. As in 2004, this likely reflects the limited evidence base and highlights the need for appropriate studies to inform best practice.

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Table 1 Investigation used to establish a GOR diagnosis by percentage of units

Trial of therapy	58%
pH study	24%
GI contrast study	23%
MMI/pH study	6%
Abdominal ultrasound	3%
Gastro-oesophageal scintigraphy	2%

Table 2 Treatment used by percentage of units

Gaviscon	60%
Ranitidine	53%
Thickening agents	27%
Proton pump inhibitors	23%
Domperidone	22%
Erythromycin	6%