# Cross-Over Trial of Treatment for Bradycardia Attributed to Gastroesophageal Reflux in Preterm Infants

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**Objective** To determine whether anti-reflux medications reduce bradycardia episodes attributed to clinically suspected gastroesophageal reflux (GER).

**Study design** We conducted a masked trial comparing metoclopramide, 0.2 mg/kg/dose q 6 hours, and ranitidine, 2 mg/kg/dose q 8 hours, with saline placebo. Each infant served as his own control. Preterm infants having >3 bradycardia episodes per 2 days were eligible if the clinician intended to begin anti-reflux medications for bradycardia attributed to GER.

**Results** The mean (SD) birth weight was 1238 (394) g and gestational age was 29 (3) weeks. Eighteen infants were enrolled at 35 (22) days of age. There were 4.6 (3.1) and 3.6 (2.7) bradycardia episodes per day in the drug and placebo periods, respectively. The mean difference (drug minus placebo) was 0.94 (95% CI, 0.04 to 1.95) ($P$ = .04 by $t$ test). There was a decrease in bradycardia episodes over time ($P$ < .001 by nonparametric repeated-measures analysis of variance).

**Conclusions** Anti-reflux medications did not reduce, and may have increased, bradycardia episodes in preterm infants with GER. Because there was an improvement of bradycardia episodes over time, unrelated to treatment, unmasked therapeutic trials of medications are likely to lead to misleading conclusions. *(J Pediatr 2009;155:516-21)*.

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Gastroesophageal reflux (GER), commonly defined as the involuntary passage of gastric contents into the esophagus, has been reported to occur in more than 85% of preterm infants.[1] In some infants, GER can be severe enough to cause gastroesophageal reflux disease (GERD), which results in malnutrition, esophagitis, or respiratory disease.[2]

Claims have been made since the 1970s that apnea in preterm infants could be caused by GER.[3,4] Apnea and bradycardia are very common in preterm infants; episodes frequently occur during and after feeding when GER is also frequent.[5] Apnea and bradycardia occurring around feedings might be causally related to GER by the mechanism of refluxate traveling up the esophagus, blocking the airway, and causing an obstructive apnea and subsequent bradycardia. Another proposed mechanism to link these events is the laryngeal chemoreflex, which causes respiratory pauses and airway closure immediately after regurgitation to the upper airway.[6] However, numerous observational studies have failed to demonstrate a temporal relationship between GER events and apnea.[7]

Common diagnostic approaches to GER include the upper gastrointestinal series (UGI) and the pH probe study. The UGI, which consists of radiographs taken after contrast material is infused or swallowed into the stomach, is neither sensitive nor specific for the diagnosis of GER.[8] The pH probe study, which is the traditional gold standard for diagnosing GERD, monitors the frequency and duration of acid reflux in the distal esophagus. However, the pH probe study has been criticized because preterm infants may have insufficient gastric acid to allow detection of acid reflux into the esophagus and because it may be performed in a brief time period (8 hours) in the neonatal intensive care unit (NICU). For these reasons, the North American Society of Pediatric Gastroenterology and Nutrition has recommended, for term infants, a "trial-limited medical therapy for GER… for determining if GER is causing a specific symptom."[8] However, a recent retrospective observational study by Kimball et al[9] has shown that anti-reflux medications did not reduce the frequency of apnea in premature infants. A recent systematic review has determined that current literature is insufficient to either support or oppose the use of metoclopramide for GERD in infants.[10] Despite the uncertainty in efficacy, adverse effects, and lack of evidence to support a causal relationship between GER and respiratory symptoms in preterm infants, prokinetic drugs (including metoclopramide) and $H_2$ receptor blocking agents (including ranitidine) are commonly used in preterm infants.[11] Approximately 25% of extremely low birth weight infants were discharged from the hospital with antireflux medications.[12]

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| GER | Gastroesophageal reflux |
| GERD | Gastroesophageal reflux disease |
| HR | Heart rate |
| IVH | Intraventricular hemorrhage |
| NCPAP | Nasal continuous positive airway pressure |
| NICU | Neonatal intensive care unit |
| UGI | Upper gastrointestinal series |

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There have been no prospective randomized trials of treatment for GERD in preterm infants with or without apnea and bradycardia. The purpose of our study was to determine whether anti-reflux medications reduce bradycardia attributed to the clinical diagnosis of GER.

## Methods

Infants with bradycardia attributed to GER were prospectively recruited in the NICU at Children's Memorial Hermann Hospital in Houston, Texas. The inclusion criteria were gestational age at birth <37 weeks and corrected gestational age at enrollment <44 weeks, a nasal clinical diagnosis of GER and bradycardia attributed to GER by clinicians, attending physician planning to begin anti-reflux medications, clinicians willing to maintain the same regimen for the 2-week study duration if the infant was on nasal continuous positive airway pressure (NCPAP) or methylxanthines, stable feeding regimen (per kilogram volume and feeding intervals), and at least 2 episodes of bradycardia in the past 3 days. Infants were excluded if they were receiving mechanical ventilation, had a history of congenital neurological defect, or if discharge was anticipated within 2 weeks. Approval for the study was obtained from the institutional review board at the University of Texas Health Science Center at Houston. Written informed parental or legal guardian consent was obtained for each patient before random assignment.

### Intervention

A randomized, controlled, masked cross-over study was performed. Each infant was randomly assigned to 1 of 2 study groups. Study group assignment (order of medication and placebo administration) was determined by blocked random number generation. A research pharmacist assigned the study group for each patient at the time of enrollment. Investigators, clinicians, and parents were all blinded to the group assignment during the study period.

The "drug first" group received a 3-day course of anti-reflux medications followed by a 7-day course of placebo and then a 4-day course of anti-reflux medications. The "placebo first" group received a 3-day course of placebo followed by a 7-day course of anti-reflux medications and then a 4-day course of placebo. To allow for a period of washout between the drug regimens, outcomes were not assessed for the initial 24 hours of the second and third time periods.

Study medications were administered by nipple or orogastric tube. Metoclopramide was given as a dose of 0.2 mg/kg per dose every 6 hours. The first dose of metoclopramide was given with the first feeding after enrollment. Ranitidine was given as a dose of 2 mg/kg per dose every 8 hours. The first dose of ranitidine was given at the same time as the first dose of metoclopramide. Intravenous preparations were used because they are clear and colorless. Saline placebos of the same volume and color were administered during the placebo periods.

At the end of the study period for each infant, after the study outcome data were summarized for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant. The summary of bradycardia episodes during the drug and placebo periods was then reviewed with the infant's physician(s) so that the information about the infant could be used for subsequent clinical management. This approach for making therapeutic decisions in individual patients has been described as an "N of 1" trial.[13]

### Outcomes

The primary study outcome was the number of bradycardia episodes per day during the drug and placebo periods for each infant. Bradycardia episodes were identified by telemetry and by nursing documentation. For the purposes of this study, a bradycardia event was defined as a heart rate (HR) <80 for >5 seconds. For each day of the study, 1 of the investigators reviewed the telemetry to identify and quantify bradycardia episodes that met the study definition. A heart rate ≤80 was identified by R-R intervals that averaged ≥0.75 seconds for a duration of 5 seconds. Any episode prompting intervention (stimulation or mask ventilation) by the nursing staff was included as a study bradycardia event, even if it did not meet the above telemetry criteria. Bradycardia events without intervention that were recorded in the nursing record but not verified by telemetry were not included as study bradycardia events.

### Co-interventions

Clinicians were asked not to make changes in feeding regimens (continuous versus bolus, intragastric versus transpyloric) or in specific treatments for apnea/bradycardia (methylxanthines or NCPAP) during the 2-week study period. Increasing the volume of feedings and number of nipple feedings was allowed. Other aspects of medical management were left to the discretion of the clinicians managing the infants.

### Sample Size

There were limited available published data from which to project the anticipated number of bradycardia episodes per day for infants enrolled in this study. A somewhat arbitrary original sample size of 34 was calculated to detect a mean decrease in bradycardia episodes of 2 per day between the placebo and drug periods with 80% power using a standard deviation of 4 for the difference.[14] Because of slower than anticipated enrollment and a planned replacement of the NICU telemetry system, after 3½ years of enrollment, the study plan was revised to enroll as many infants as feasible before March 1, 2008.

### Data Management and Statistical Analysis

Study data items were identified and defined in writing before enrollment began. Data were ascertained by chart and telemetry review by 1 of the investigators. For the primary comparison, a within-subject paired analysis (paired *t* test) was performed for the comparison of bradycardia episodes per day between the medication and placebo periods. The