ANESTHESIOLOGY

Ultrasound Evaluation of Gastric Emptying Time in Healthy Term Neonates after Formula Feeding

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ABSTRACT

Background: The current American Society of Anesthesiologists fasting guideline for formula-fed infants in the periprocedural setting is 6 h. Prolonged fasting in very young infants is associated with an increased risk for hypoglycemia and dehydration as well as patient discomfort and patient/parental dissatisfaction. This study aimed to determine the time to gastric emptying in healthy neonates after formula feeding by serially evaluating the gastric antrum with ultrasound. The authors hypothesized that gastric emptying times in formula-fed neonates are significantly shorter than the current 6 h fasting recommendation.

Methods: After institutional review board approval and written informed parental consent, ultrasound examination was performed in healthy full-term neonates before and after formula feeding at 15-min intervals until return to baseline. Ultrasound images of the gastric antrum were measured to obtain cross-sectional areas, which were then used to estimate gastric antral volumes.

Results: Forty-six of 48 recruited neonates were included in the final analysis. Gastric emptying times ranged from 45 to 150 min and averaged 92.9 min (95% CI, 80.2 to 105.7 min; 99% CI, 76.0 to 109.8 min) in the overall study group. No significant differences were found in times to gastric emptying between male and female neonates (male: mean, 93.3 [95% CI, 82.4 to 104.2 min]; female: mean, 92.6 [95% CI, 82.0 to 103.2 min]; P = 0.930) or those delivered by vaginal *versus* cesarean routes (vaginal: mean, 93.9 [95% CI, 81.7 to 106.1 min]; cesarean: mean, 92.2 [95% CI, 82.5 to 101.9 min]; P = 0.819).

Conclusions: These results demonstrate that gastric emptying times are substantially less than the current fasting guideline of 6 h for formula-fed, healthy term neonates.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The temporal kinetics of gastric emptying in formula-fed neonates are incompletely understood
- Currently, American Society of Anesthesiologists guidelines recommend 6 h of fasting in formula-fed neonates and infants before anesthesia

What This Article Tells Us That Is New

- Serial ultrasound imaging of the gastric antrum in healthy term neonates after formula feeding reveals gastric emptying times ranging from 45 to 150 min
- These observations suggest that preanesthesia fasting of healthy term neonates could be substantially shorter than is currently recommended

Preprocedural fasting in patients of all ages is recommended as a patient safety measure to mitigate the risks of pulmonary aspiration, an infrequent but potentially devastating complication during anesthesia.[1] The American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Practice Guidelines for fasting in elective procedures recommend that in formula-fed infants, fasting should be "from intake of infant formula at least 6 h before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia." For breastfed infants, the recommendations advise fasting "from intake of breast milk at least 4 h before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (*i.e.*, monitored anesthesia care)." These guidelines require a much longer fasting time than the usual interval at which infants are fed, which is typically every 2.5 to 3 h on demand.

Currently, for both breastfed and formula-fed infants, the level of evidence supporting the fasting guidelines is considered to be category C3 (equivocal literature from observational studies reporting inconsistent findings or do

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 823. This article has a related Infographic on p. A21. This article has an audio podcast. This article has a visual abstract available in the online version. The work presented in this article has been presented as "Ultrasound Evaluation of Gastric Emptying Time in Neonates" at the 23rd Annual Academic Evening at the Columbia University Irving Medical Center (New York, New York), September 8, 2020. J.J.L. and J.C.P. contributed equally to this article.

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not permit inference regarding benefit or harm) regarding gastric volume and pH, and category D (insufficient evidence from literature) with regard to risks of pulmonary aspiration. The patient safety issues that have not been considered in these recommendations are the physiologic effects of prolonged fasting in very young infants. While many practitioners encourage babies to have clear fluids up to 2 h before the procedure, neonates and young infants may not accept clear fluids. Prolonged fasting without clear fluid supplementation could therefore seriously increase the risks of dehydration in this vulnerable population.

Prolonged fasting could also lead to hypoglycemia in the very young due to the lack of glycogen stores,[2] immaturity of gluconeogenic pathways, and inadequate ketogenic responses to hypoglycemia.[3] A high incidence of hypoglycemia has been documented for young children who were fasted preoperatively by Thomas, who found 28% of children younger than 47 months of age and weighing less than 15.5 kg who had fasted preoperatively became hypoglycemic, some profoundly.[4] Hypoglycemia and dehydration may manifest as hemodynamic instability at the time of anesthesia induction and cause significant harm.[5–7] Finally, prolonged durations of fasting could result in high rates of noncompliance and may thus compromise the goals of aspiration prevention and patient safety.

Recently, several studies have documented the use of gastric ultrasound as a valid tool for the assessment of antral area in adults and older children.[8–14] Specifically, the area of the gastric antrum has been shown to accurately predict gastric volume.[15,16] The aim of this study was to generate evidence to support or refute current preprocedural *non per os* (NPO) guidelines for neonates by determining gastric emptying times using ultrasound of the gastric antrum after formula feeding, which would optimize patient safety and well-being in addition to patient/parental satisfaction. Our hypothesis is that the gastric emptying time in healthy neonates after formula feeding is less than the current guideline of 6 h of fasting.

Materials and Methods

This study was approved by the Columbia University Institutional Review Board (May 2015; AAAP6304). This clinical trial was registered in the ClinicalTrials.gov database on January 28, 2016 (NCT02665923; principal investigator: L.S. Sun). A data analysis plan was written and posted on a publicly accessible server (ClinicalTrials.gov), and a statistical analysis plan was written and filed with a private entity (Anesthesia Patient Safety Foundation, Rochester, Minnesota) before data were accessed. All mothers on the postpartum well-baby units at the Allen Hospital (New York, New York) and Morgan Stanley Children's Hospital of New York Presbyterian Hospital (New York, New York) were screened to identify healthy full-term (postmenstrual age greater than or equal to 36 weeks) neonates aged 0 to 5 days who were formula-fed for possible recruitment. Exclusion criteria included individuals who (1) required resuscitation at delivery; (2) were admitted to the neonatal intensive care unit; (3) were diagnosed with gastroesophageal reflux or other feeding difficulty; or (4) received any medication known to accelerate or delay gastric emptying, including but not limited to opioid-containing medications and antacids.

Study details were discussed with the mother and/or father, and then written informed consent was obtained. Demographic information and clinical history were recorded from the electronic medical record. Participants underwent an initial ultrasound scan immediately before feeding to determine the baseline gastric antral cross-sectional area, then fed formula. This feeding volume was recorded. After feeding, serial ultrasounds of the gastric antral area were obtained every 15 min until the antral area returned to "baseline," which was defined as within 10% of prefeeding measurements. The time lapse from gastric antral cross-sectional area before feeding until its return to baseline was considered the gastric emptying time, which was the primary outcome of this study; therefore, each participant acted as his or her own control for the sonographic measurements.

The study was designed to obtain data for further analysis at later ages as secondary outcomes. However, the current study focuses on reporting the findings in neonates and the primary outcome.

Ultrasound Measurements and Calculations

Gastric antral ultrasound was performed using the SonoSite Edge II (FujiFILM SonoSite, Inc., USA) with a high-frequency linear transducer in the sagittal plane with patients positioned in the right lateral decubitus position. The transducer was tilted and rotated as necessary to visualize a cross-sectional view of the antrum immediately adjacent to the left lobe of the liver (fig. 1).

Gastric antral cross-sectional area was measured using the two-diameter method where two perpendicular diameters (A, B) were measured and then, assuming a perfect elliptical shape, the cross-sectional area was calculated by the formula for area of an ellipse: cross-sectional area = $\frac{1}{4}AB\pi$ (representative measurements shown in fig. 1). Cross-sectional area was then used to estimate the gastric antral volume using the following formula: gastric antral volume = (weight) × [0.009 × cross-sectional area − 1.36]. This formula is derived from the model created by Schmitz *et al.*,[16] the only model created for pediatric patients. All measurements were taken by four trained study investigators (A.D., A.S., R.H., N.A.D.) and were later reviewed by a pediatric radiologist coinvestigator (J.H.S.).

Statistical Analysis

All statistical analyses were performed in Excel 15.23 (Microsoft [USA] Excel 2016) and RStudio 1.2.5019

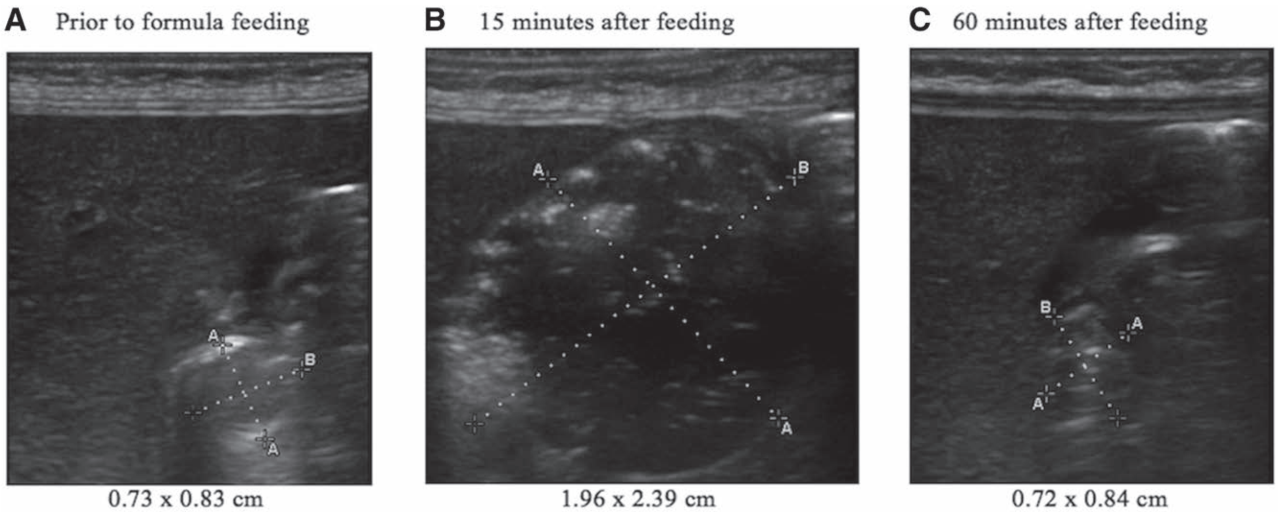

Fig. 1. Sagittal antral views in the right lateral decubitus in a representative study participant. Images were taken immediately before feeding (*A*), then repeated every 15 min after formula feeding (*B*) until gastric antral cross-sectional area returned to baseline, which was at 60 min (*C*). Calipers labeled A and B = 2 perpendicular diameters used to calculate cross-sectional area.

(RStudio, Inc. [USA] 2009 to 2019). A histogram was used to assess data distribution. Descriptive analyses of demographic and clinical data were conducted. Continuous data are reported as mean ± SD. Categorical data are reported as counts and percentages. Data for time to gastric emptying are reported as mean ± SD, 95% CI, 99% CI, median (interquartile range), and range (minimum to maximum). We compared the mean gastric emptying time in neonates to 6 h of fasting by using a one-sided one-sample *t* test. Preplanned subgroup analyses by sex and mode of delivery were also conducted. The Welch *t* test for unequal variance was used to compare two sample means for continuous data, and the Fisher exact test was used to compare categorical data in these subgroups. Pearson correlation coefficients were used to identify any correlation between participant age, gestational age at birth, weight, amount fed, baseline gastric antral cross-sectional area, and time to gastric emptying. A *P* value less than 0.05 was considered statistically significant. An average trendline for the time course of gastric emptying was plotted by calculating the average of gastric antral cross-sectional area measurements for all 46 participants at each 15-min interval from prefeeding until return to baseline (fig. 2).

Sample size needed was calculated based on our pilot study data with seven neonates that had a mean gastric emptying time of 62 ± 16 min. With 30 neonates, there would be 80% power to detect a difference of 8.5 min between the null hypothesis mean (360 min based on current NPO guidelines) and the alternative hypothesis mean (351.5 min, and an assumed SD of 16) at a significance level of 0.05 using a two-sided one-sample *t* test. Assuming the same SD of 16, the sample size of 50 neonates would detect a difference of 6.5 min in mean gastric emptying times at $P = 0.05$, or a difference of 8.0 min at the more stringent $P = 0.01$.

Results

Forty-six of the total 48 recruited neonates were included in the final analysis and had complete data for ultrasound measurements. Two participants were excluded because they were unable to complete their studies, and the last measurements were not considered to be a return to baseline. One participant was discharged home, and the study was terminated after the 75-min time point; the other was taken for testing before they were able to complete the study, and the study was terminated after the 105-min time point.

Maternal and neonatal demographic characteristics of the enrolled study group are summarized in table 1. There was an equal distribution of sex in the overall study group (males: 23 of 46 [50.0%]; females: 23 of 46 [50.0%]). Ages of participants were 1.5 ± 0.7 days. Their weights were 3.3 ± 0.5 kg, and gestational ages were 39.4 ± 1.4 weeks. Apgar score at 1 min was 8.6 ± 0.1 and at 5 min, 9.0 ± 0.2. The majority (91.3%) of neonates were of Hispanic race/ethnicity (42 of 46), and 58.7% were delivered *via* cesarean section (27 of 46).

Maternal gravidity was 2.9 ± 1.9, and parity was 2.0 ± 1.2. In close to half of the mothers (22 of 46 [47.8%]), health issues were present. The volume of formula fed in the participants was 29.7 ± 10.6 ml (9.0 ± 3.2 ml/kg), with time elapsed since feeding before study scan averaging 3.1 ± 0.8 h. Overall, gastric emptying times ranged from 45 to 150 min

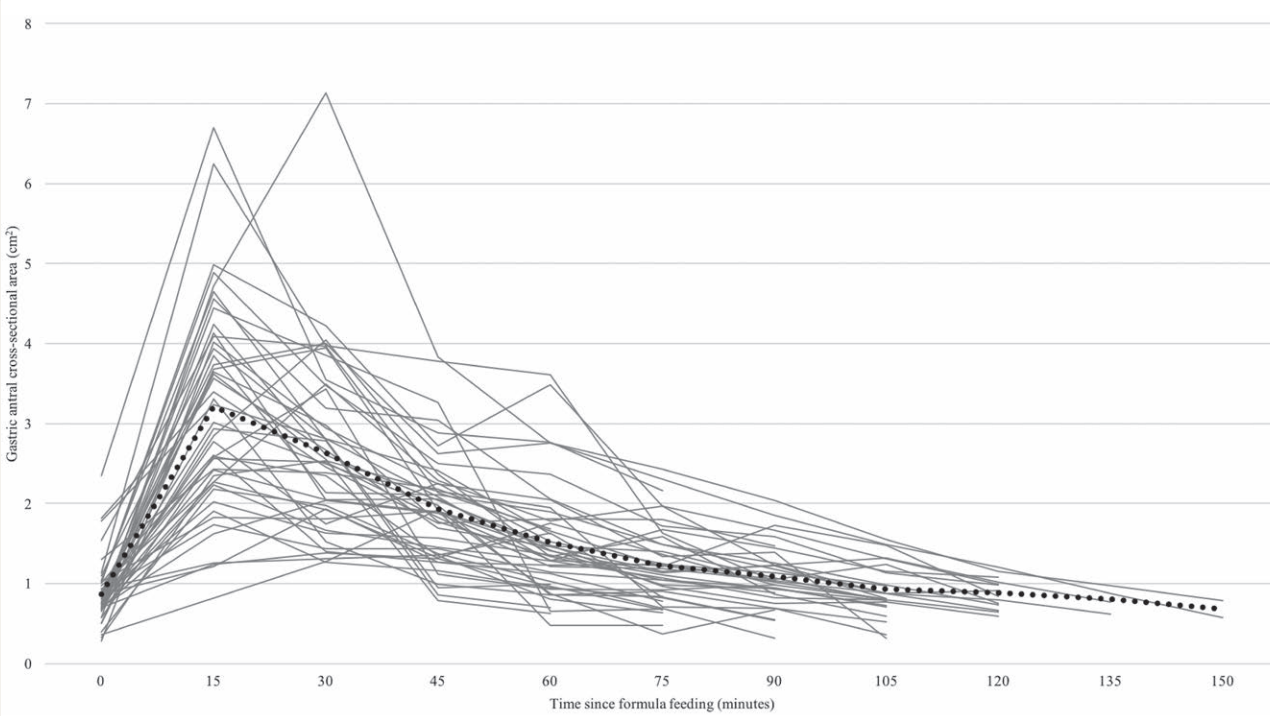

Fig. 2. Time course of gastric emptying. Each *line* depicts the gastric antral cross-sectional area data pre- and postfeeding until return to baseline for each study participant (n = 46). The average trendline is represented by the *black dotted line*.

with a mean of 92.9 min (95% CI, 80.2 to 105.7 min; 99% CI, 76.0 to 109.8 min). The median gastric emptying time was 90 min (interquartile range, 75 to 105 min; table 2). Gastric emptying time was significantly less than the current NPO guideline of 6 h for formula ($P < 0.0001$).

Subgroup analyses by sex and mode of delivery were also conducted. Female participants were older than male participants (1.7 ± 0.7 days *vs.* 1.3 ± 0.7 days). Apgar scores at 1 min were lower in neonates delivered by cesarean section compared with the vaginal route (8.3 ± 1.4 *vs.* 9.0 ± 0.0). Otherwise, there were no substantial differences in mother or participant characteristics between these subgroups.

Gastric emptying times were not found to be significantly different between male (mean, 93.3 [95% CI, 82.4 to 104.2 min]) and female neonates (mean, 92.6 [95% CI, 82.0 to 103.2 min]; $P = 0.930$) or those delivered by vaginal (mean, 93.9 [95% CI, 81.7 to 106.1 min]) and cesarean routes (mean, 92.2 [95% CI, 82.5 to 101.9 min]; $P = 0.819$). No significant correlation was found between participant age ($P = 0.739$), gestational age at birth ($P = 0.138$), weight ($P = 0.609$), amount fed ($P = 0.294$), and time to gastric emptying using the Pearson correlation. There was a moderate negative correlation between baseline antral cross-sectional area and time to gastric emptying (Pearson correlation coefficient = −0.35; $P = 0.018$). The overall time course of gastric emptying for each individual study participant and the average trendline are depicted in figure 2.

Discussion

In this study, we assessed gastric emptying times in healthy neonates in order to provide evidence to support or refute current NPO guidelines for formula as established by the ASA. We report gastric emptying times using serial ultrasonography in the neonatal population. In this well-powered clinical trial, we found the time to return to baseline antral cross-sectional area was 92.9 ± 42.6 min in 46 healthy full-term neonates aged 0 to 5 days. The upper range of gastric emptying time was 150 min, while the upper limit at the 99% CI was 109.8 min. There were no significant differences in gastric emptying time in subgroup analyses according to sex or mode of delivery. These findings suggest that the current fasting guidelines may be more stringent than necessary by more than 3 h.

This study's results are concordant with a recent report from Europe published by Beck *et al.* that evaluated 22 preterm infants who received either breast or formula milk by hourly sonographic measurements and calculated a mean gastric emptying time of 218 min, which is less than the current national fasting guideline of 4 h for any milk composition in Germany.[17] When compared to preterm infants, the current study suggests that full-term neonates may exhibit even more rapid gastric emptying.

The ultrasound assessment of gastric antral area has been established as a reliable and reproducible method of

Table 1. Demographic and Clinical Characteristics of the Study Group

	All (N = 46)	Male (n = 23)	Female (n = 23)	Vaginal (n = 19)	Cesarean (n = 27)
Age, days*	1.5 ± 0.7	1.3 ± 0.7	1.7 ± 0.7	1.4 ± 0.7	1.6 ± 0.7
Sex					
Male (%)	23 (50.0)			9 (47.4)	14 (51.9)
Female (%)	23 (50.0)			10 (52.6)	13 (48.2)
Race/ethnicity					
White (%)	1 (2.2)	1 (4.3)	0 (0)	0 (0)	1 (3.7)
Hispanic (%)	42 (91.3)	21 (91.3)	21 (91.3)	17 (89.5)	25 (92.6)
Black (%)	4 (8.7)	1 (4.3)	3 (13.0)	2 (10.5)	2 (7.4)
Asian (%)	2 (4.3)	1 (4.3)	1 (4.3)	1 (5.3)	1 (3.7)
Weight, kg*	3.3 ± 0.5	3.5 ± 0.6	3.2 ± 0.5	3.4 ± 0.5	3.3 ± 0.6
Gestational age at birth, weeks*	39.4 ± 1.4	39.5 ± 1.3	39.3 ± 1.6	39.7 ± 1.5	39.2 ± 1.4
Apgar scores*					
1 min	8.6 ± 0.1	8.4 ± 1.5	8.7 ± 0.7	9.0 ± 0.0	8.3 ± 1.4
5 min	9.0 ± 0.2	9.0 ± 0.0	9.0 ± 0.3	9.1 ± 0.2	9.0 ± 0.2
Mode of delivery					
Vaginal (%)	19 (41.3)	9 (39.1)	10 (43.3)		
Cesarean (%)	27 (58.7)	14 (60.9)	13 (56.5)		
Maternal characteristics					
Gravidity*	2.9 ± 1.9	2.8 ± 2.2	2.9 ± 1.7	2.4 ± 1.4	3.2 ± 2.2
Parity*	2.0 ± 1.2	1.7 ± 1.3	2.2 ± 1.2	1.6 ± 0.9	2.0 ± 1.4
Maternal health issues (%)	22 (47.8)	13 (56.5)	9 (39.1)	6 (31.6)	16 (59.3)
Time since last feeding, h*	3.1 ± 0.8	3.1 ± 0.9	3.1 ± 0.5	2.9 ± 0.5	3.2 ± 0.9
Amount of last feeding, ml; ml/kg*	30.1 ± 10.6; 9.0 ± 2.9	29.3 ± 11.0; 8.4 ± 2.8	30.8 ± 10.4; 9.6 ± 2.9	30.5 ± 12.5; 9.1 ± 3.4	29.8 ± 9.3; 9.0 ± 2.6
Amount of current feeding, ml; ml/kg*	29.7 ± 10.6; 9.0 ± 3.2	28.0 ± 8.4; 8.2 ± 2.7	31.4 ± 12.5; 9.8 ± 3.5	28.6 ± 10.9; 8.6 ± 3.0	30.5 ± 10.6; 9.3 ± 3.3
Baseline gastric antral cross-sectional area, cm^2*	0.9 ± 0.4	0.9 ± 0.3	0.9 ± 0.5	0.8 ± 0.3	0.9 ± 0.4

Summary of the overall study population and by subgroups (sex and mode of delivery) is presented here. Numbers for race/ethnicity may exceed the total n, as some patients fall into multiple designations.

*Values are mean ± SD.

Table 2. Primary Outcome Analysis of Gastric Emptying Time

	All (N = 46)	Male (n = 23)	Female (n = 23)	*P* Value	Vaginal (n = 19)	Cesarean (n = 27)	*P* Value
Time to gastric emptying, min							
Mean ± SD	92.9 ± 42.6	93.3 ± 25.2	92.6 ± 24.6	0.930	93.9 ± 25.4	92.2 ± 24.5	0.819
95% CI	80.2–105.7	82.4–104.2	82.0–103.2		81.7–106.1	82.5–101.9	
99% CI	76.0–109.8	78.5–108.1	78.1–107.1		71.1–110.7	79.1–105.3	
Median (interquartile range)	90 (75–105)	90 (75–112.5)	90 (75–105)		90 (75–105)	90 (75–105)	
Minimum, maximum	45, 150	45, 135	60, 150		45, 150	45, 135	

Data for time to gastric emptying in the overall study group and by subgroups. No significant differences in primary outcome were found according to sex or mode of delivery.

determining gastric volume with high intra- and interrater reliability.[18] It has also been shown to correlate closely with scintigraphic measurement, an invasive definitive standard using radioactive material,[19] and most studies report a linear correlation between antral cross-sectional area and gastric antral volume with Pearson correlation coefficients ranging from 0.6 to 0.91, particularly in the right lateral decubitus position.[20] Gastric content and volume assessment may serve as a new point-of-care ultrasound application to help determine aspiration risk, particularly in urgent or emergent situations and for patients with certain comorbidities.

While the goal of current fasting guidelines is to reduce the occurrence of pulmonary aspiration during the periprocedural period, the reported incidence of pulmonary aspiration, in addition to its associated morbidity and mortality, is extremely low.[21–23] On the other hand, prolonged fasting has frequently been associated with volatile intraoperative hemodynamics, hypoglycemia, and significant preoperative irritability. A recent study comparing the effects of optimized fasting times in children younger than 36 months of age found lower ketone body concentration, decreased incidence of hypotension, and an increase in mean arterial pressure after induction of anesthesia with no reported pulmonary aspiration events.[24]

Similarly, Andersson *et al.* examined the effects of allowing 10,015 pediatric patients to drink clear fluids until called to the operating room. They found an incidence of pulmonary aspiration of 0.03%, which is comparable to the reported incidence when following traditional guidelines.[25] A large multicenter study recently concluded that NPO status is not an independent predictor of major complications or aspiration.[26]

Liberalizing fasting times may not only improve patient/parental satisfaction but also minimize the risks of hypoglycemia and dehydration for the very young infant. In addition, it could also improve workflow in procedural areas and in the operating rooms by avoiding excessive time required to achieve desired NPO status.

This study has several limitations. First, only formula-fed babies were included due to the difficulty of quantifying the volume of breast milk ingested in nursing neonates. Many neonates are breastfed, and therefore the results of this study cannot necessarily be extrapolated to these babies. Breast milk has been shown to empty more rapidly than formula[27]; thus, while definitive studies need to be done for breastfed babies, it can reasonably be inferred that the time to gastric emptying may be far less than 3 h given our findings.

Second, the model used to calculate gastric antral volume from cross-sectional area was first created by Schmitz *et al.* for pediatric patients aged 6 to 10 yr.[16] Although the model was not specifically validated in very young infants, gastric emptying time in this study uses return to baseline as the endpoint, thus providing a consistent approach to the assessment of gastric emptying times.

Third, the amount of formula ingested was not standardized in this study. However, in our analysis, we did not find a significant correlation between the amount ingested and gastric emptying time. Fourth, our study population was predominantly of Hispanic race/ethnicity. While generalizing the results must be cautiously applied to the ethnically and racially diverse U.S. population, it is important to note that there have been no ethnic or racial differences reported in gastric emptying time. Finally, this study specifically evaluated gastric emptying times in healthy neonates aged 0 to 5 days. It is unclear whether findings from this study may be generalizable to neonates requiring surgery with underlying pathologies or to older infants.

Future research directions would include larger neonatal ultrasound studies to corroborate any evidence from our current study and would be powered to detect rare pulmonary aspiration events. Another definitive study would compare existing and new NPO guidelines, as proposed by findings from this trial, in an actual perioperative setting using indicators such as NPO times, blood glucose levels, and quantitative measures of volume status. More data are needed to determine whether reduced fasting would have any effect on perioperative outcomes.[28]

In conclusion, gastric emptying time, as assessed by serial ultrasound after formula feeding in healthy full-term neonates, was determined to never exceed 2.5 h using upper range or 99% CI. Currently, the ASA recommends a preprocedural fasting time of 6 h for formula feeding. This study suggests that abbreviating the fasting guidelines in formula-fed neonates requiring anesthesia and sedation may need to be considered for the optimization of patient safety, comfort, and satisfaction.

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Competing Interests

The authors declare no competing interests.

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