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ORIGINAL ARTICLE

The impact of feeding interval on feeding outcomes in very low birth-weight infants

SB DeMauro[1], S Abbasi[2] and S Lorch[1]

[1]The Children's Hospital of Philadelphia and The University of Pennsylvania, Philadelphia, PA, USA and [2]Pennsylvania Hospital and The University of Pennsylvania, Philadelphia, PA, USA

Objective: Test the hypothesis that very low birth-weight (VLBW) infants fed every 2 h (q2) are able to reach full enteral feedings more quickly than infants fed every 3 h (q3).

Study Design: We performed a retrospective cohort study comparing q2 infants ($n = 103$) with q3 infants ($n = 251$). The primary outcome was days from start of a feeding advance to full feedings (120 ml per kg per day). Multivariable regression models were used to control for maternal and perinatal factors that preceded the initiation of the feeding advance.

Result: Infants fed q2 reached full feedings 2.7 days sooner than q3 infants (95% confidence interval (CI) 1.5, 3.9). After adjustment for confounders, q2 infants reached full feedings 3.7 (95% CI 1.6, 5.9) days more quickly. Infants fed q3 were more likely to receive >28 days of parenteral nutrition (odds ratio (OR) 4.7; 95% CI 1.5, 14.4), and were more likely to have feeds held for ⩾7 days (OR 4.7, 95% CI 1.9, 11.7).

Conclusion: VLBW infants demonstrate improved feeding tolerance when fed more frequently.
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Keywords: premature infant; feeding regimen; feeding tolerance

Introduction

The decision to initiate enteral feedings in a very low birth-weight (VLBW) infant has many components including timing, type of feed, starting volume and feeding interval.[1–8] Little evidence is available to guide these decisions, especially about feeding interval. Several small studies and a systematic review suggest that intermittent bolus feedings—compared with continuous feedings—improve feeding tolerance and growth in VLBW infants.[8–11] Bolus feedings stimulate maturation of hormone secretion and motility in the premature gastrointestinal tract.[12–14] Rapidly administered boluses decrease intestinal motor activity, while slowly administered boluses increase activity.[15,16] Feeding volume and infusion rate have been implicated in large post-prandial hormonal surges in preterm infants, but the exact relationships between feedings, hormonal surges and gastrointestinal maturation remain unknown.[13,16]

The American Academy of Pediatrics policy statement on breastfeeding states that full-term infants should eat every 2 to 3 h.[17] Nevertheless, preterm infants are routinely expected to tolerate large-volume feedings every 3 to 4 h. Less frequent feedings decrease nursing workload and infant handling. On the other hand, feedings every 2 h (q2) can be 1/3 smaller than feedings every 3 h (q3). If intolerance is related to volume, the q2 schedule should allow patients to reach full feeds more quickly.

Only one small study has evaluated the association between feeding interval and feeding tolerance in VLBW infants.[18] With fewer than 50 infants per group, the study was underpowered to find a significant difference between q2 and q3 feeds on days to achieve full feedings. Therefore, the optimal feeding interval for VLBW infants remains to be determined. We conducted this retrospective study to investigate the impact of q2 versus q3 boluses on the length of time VLBW infants required to reach full volume enteral feedings.

Methods

This retrospective cohort study was performed at the neonatal intensive care units of the Hospital of the University of Pennsylvania and Pennsylvania Hospital. The study was approved by the Institutional Review Boards of the Hospital of the University of Pennsylvania, Pennsylvania Hospital, and The Children's Hospital of Philadelphia.

Data collection

Infants with birth weight 500 to 1500 g and admitted consecutively between January 1, 2004 and December 31, 2005 were identified using the hospitals' internal databases. Patients were excluded for outborn status, major congenital malformation, transfer out of the study hospital before discharge, or death or intestinal perforation before the initiation of feeding.

Correspondence: Dr SB DeMauro, The Children's Hospital of Philadelphia, Division of Neonatology, 34th and Civic Center Boulevard, Main Building, 2nd Floor, Room 2425, Philadelphia, PA 19104, USA.
E-mail: demauro@email.chop.edu
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Three types of data were collected from patient charts. First, we collected potentially confounding perinatal data including birth weight, gestational age, race, sex, Apgar scores and antenatal steroid exposure. Second, we collected information about the neonatal course, including indomethacin therapy for patent ductus arteriosus, episodes of sepsis and necrotizing enterocolitis (NEC), duration of pressor support, intubation, and central catheters, length of stay and death. Finally, we collected data about enteral feedings. These data included type of enteral feeding used, day of feeding initiation, days of trophic feedings, rate of increase, daily feeding volumes, duration of total parenteral nutrition (TPN) and daily weights.

Outcome and confounding variable definitions

The primary endpoint was the number of days from initiation of a feeding advance until attainment of full enteral feeding, defined as 120 ml per kg per day of formula or breast milk. Intake was calculated by dividing the total volume of enteral feedings administered over a 24-h period by the weight. Daily weights were used after the infant exceeded birth weight. Days of trophic feedings were excluded. Trophic feedings were defined as $\leqslant$20 ml per kg per day divided q3 or 2 ml per kg q2 for 12 feeds.[7] If feedings were stopped for >24 h and then restarted during the period of trophic feedings, then the trophic feeding period was considered to be the total days of feedings before initiation of feeding advance, excluding the nil per os (NPO) days.

Secondary outcomes were the total number of days feeds were held and the number of days of TPN. The total days feedings were held was calculated as the total hours of all NPO periods between initiation of trophic feedings and reaching full feedings, divided by 24. Feedings were held for any of the following reasons at the clinician's prerogative: feeding intolerance, presumed or confirmed sepsis or NEC, hypotension, or medical or surgical treatment of patent ductus arteriosus.

Apgar scores were categorized as low (0 to 3), middle (4 to 6), or high (7 to 10). NEC was defined as stage 2 or greater, according to Bell's classification.[19] Small for gestational age was defined as birth weight <10th percentile for gestational age.[20]

Feeding regimens

Decisions about feeding, including timing of feeding initiation, q2 or q3 feeding interval, and duration of trophic feedings, were made entirely by the attending responsible for the infant's care. Importantly, no protocol dictated the choice of feeding interval. Volumes were increased by 20 ml per kg per day, unless the infant demonstrated feeding intolerance. Because of the retrospective nature of this study, feeding intolerance could not be defined *a priori*. Therefore, every episode of NPO documented in the medical record was included in the analysis. Continuous feeding regimens were reserved for infants with severe feeding intolerance. TPN was started on day of life one and continued until the infant achieved enteral feedings of 100 to 120 ml per kg per day.

Infants were categorized according to the scheduled time interval between enteral feedings. Feeding interval was determined for each day from the start of the feeding advance until full feedings were achieved. Some infants were started on a q2 schedule and then switched to q3, or vice versa. The variable of interest in this study is the interval that allowed for successful advancement to full feedings. Therefore, we counted the number of days that each interval was ordered and categorized infants according to the regimen used for the majority of days. In a secondary analysis, we used an 'intention to treat' model and categorized infants by the regimen ordered at the start of the advance.

Data analysis

Baseline maternal and neonatal characteristics and neonatal outcomes were compared between the q2 and q3 groups using standard statistical measures, including χ^2, Student's t and Wilcoxon rank-sum tests, as appropriate. P-values $\leqslant 0.05$ were considered significant. STATA/IC10.0 was used for all analyses.

For analysis of the primary outcome—days to full feedings—a multivariable linear regression model was used to adjust for significant perinatal and neonatal factors. A Cox model was not used because the data did not meet the assumption of proportional hazards. To further evaluate the relationship between gestational age and feeding interval, we stratified infants by gestational age (<28, 28 to $29^{6/7}$, 30 to $31^{6/7}$, and $\geqslant$32 weeks) and repeated bivariate and multivariable analyses of the primary outcome. For the two secondary outcomes—days of NPO and days of TPN—we dichotomized the data around a clinically relevant cutoff near the 90th percentile for each outcome (7 days for NPO and 28 days for TPN), and developed logistic regression models using these dichotomous outcomes as the dependent variables. Linear models were not used because the data were skewed to the right.

All models were constructed by backwards elimination of potential explanatory factors because of the size of the cohort. Factors known to be important confounders of many neonatal outcomes, such as gestational age, race and gender were included in the models. To improve detection of potential confounders, other variables with P-values of <0.2 in bivariate analysis were considered for inclusion in the models.[21] Some correlated explanatory variables, such as gestational age and day of life feedings were initiated, were included in the model in order to best control for differences between the study groups. NEC was not included in the models because it is in the causal pathway for the study outcomes. Nonsignificant variables were then eliminated from the model one at a time until the reduced model was statistically different from the full model by likelihood ratio tests. Center was retained in all final models to control for potential

unmeasured center differences. Before the study, we estimated that 115 patients in each group would provide 80% power to detect a 3-day difference in time to full feedings, with a s.d. of 8 days and $\alpha = 0.05$.[22] On the basis of census history, we expected to achieve this sample size with 2 years of data.

Results

During 2004 and 2005, 378 infants with birth weight 500 to 1500 g were admitted to the neonatal intensive care units at the Hospital of the University of Pennsylvania and Pennsylvania Hospital. In all, 16 infants were excluded for missing data ($n = 4$), outborn status ($n = 2$), transfer out of study hospital before discharge ($n = 2$), congenital abnormalities that could affect feeding ($n = 2$) and death or intestinal perforation before initiation of enteral feedings ($n = 6$). Evaluation of the baseline maternal and perinatal characteristics of the two infants who were transferred out of the study centers before discharge demonstrated that they were not significantly different from the included infants. The remaining 362 infants were included in the analysis.

Feeding interval groups

We classified 103 infants as q2, 251 infants as q3, and 8 infants in the continuous feeding group. Of the eight infants in the continuous feeding group, seven were switched from q3 to continuous after NEC ($n = 2$), feeding intolerance ($n = 4$) or hypoglycemia ($n = 1$). One infant was switched from q2 to continuous feedings for feeding intolerance. Because the continuous feeding group was very small, these infants were excluded from further analyses.

Baseline neonatal characteristics and demographics of the q2 and q3 groups were similar (Table 1). The q2 group was younger and smaller at birth. There were no significant differences in measures of illness severity such as rates of bloodstream infection, indomethacin therapy and corrected gestational age at discharge (Table 2). Notably, the rates of NEC were almost identical. There was no difference in the day feedings were started. The q2 group had a lower rate of exclusive breast-milk feedings, better weight gain and more days of trophics, and was receiving a lower enteral volume when TPN was discontinued (Table 2).

Primary outcome

In bivariate analysis, the q2 group required 6.7 ± 3.2 days and the q3 group required 9.4 ± 8.6 days to reach full enteral feedings, a mean difference of 2.7 days (95% CI 1.5, 3.9; $P<0.001$, Table 2).

A multivariable model of days to full feedings, adjusted for potentially confounding maternal and neonatal characteristics, was constructed (Table 3). Nonsignificant factors were eliminated from the model and, based on a likelihood ratio test, the final model was not statistically different from the full model. Although bivariate analysis demonstrated differences between the groups

Table 1 Baseline characteristics, stratified by feeding interval

Variable	*q3 (n = 251)*	*q2 (n = 103)*	P-*value*
Gestational age (weeks)	29.6 ± 2.5	28.3 ± 1.9	<0.001
Birth weight (grams)	1204 ± 233	1053 ± 162	<0.001
Male sex	126 (50%)	50 (49%)	0.78
Small for gestational age	53 (21%)	19 (18%)	0.57
Maternal age (years)	28.3 ± 6.5	28.5 ± 7.0	0.79
Cesarean section	163 (65%)	79 (77%)	0.03
Antenatal steroids	205 (82%)	83 (81%)	0.81
Pre-eclampsia	62 (25%)	27 (26%)	0.77
Maternal race			0.03
White	67 (27%)	39 (38%)	
Black	167 (67%)	53 (51%)	
Other	17 (7%)	11 (11%)	
5-min Apgar			0.12
Low (0–3)	6 (2%)	0 (0.0%)	
Middle (4–6)	25 (10%)	6 (6%)	
High (7–10)	220 (88%)	97 (94%)	

Groups compared with Student's *t*-test, Wilcoxon rank-sum test, or χ^2 test. Values are noted as mean ± s.d. or *n* (%).

Table 2 Bivariable comparisons of neonatal outcomes, stratified by feeding interval

	q3 (n = 251)	*q2 (n = 103)*	P-*value*
Neonatal Outcomes			
Necrotizing enterocolitis	31 (12%)	13 (13%)	0.94
Indomethacin therapy	103 (41%)	45 (44%)	0.65
PDA ligation	24 (10%)	8 (8%)	0.59
Days intubated	1 (0,4)	2 (0,5)	0.09
Blood stream infection	43 (17%)	19 (18%)	0.77
Death before discharge	2 (1%)	3 (3%)	0.13
Corrected gestational age at discharge	38.0 ± 5.0	37.6 ± 6.1	0.53
Central line days	10 (0, 21)	11 (8,18)	0.18
Outcomes related to feeding			
Day of life feedings were started	5.1 ± 5.6	4.7 ± 4.2	0.54
Days of trophic feedings	2 (1,4)	5 (2,6)	<0.001
Exclusive breast-milk feedings	66 (26%)	14 (14%)	0.009
Days to full feedings	9.4 ± 8.6	6.7 ± 3.2	<0.001
Daily weight gain (grams)	19.3 ± 4.1	20.5 ± 4.1	0.02
Enteral volume on day TPN was discontinued (ml per kg per day)	114 ± 21	108 ± 22	0.03
Feeds held >1 week	50 (20%)	14 (14%)	0.16
TPN for >28 days	45 (18%)	13 (13%)	0.22

Abbreviations: PDA, patent ductus arteriosus; TPN, total parenteral nutrition.
Groups compared with Student's *t*-test, Wilcoxon rank-sum test, or χ^2 test. Values are noted as *n* (%), median (interquartile range), or mean ± s.d.

in race, cesarean section rate and exclusive breast-milk feeding, these variables did not contribute significantly to the final multivariable model. We included day of life feedings were started and number of days of trophics because we believe that these variables confound the relationship between feeding interval and time to full feedings. After adjustment, q2 infants reached full feedings 3.7 days faster (95% CI 1.6, 5.9) than q3 infants. Changing trophic feedings to a dichotomous variable or including it as both a dichotomous and continuous variable did not impact these results.

Table 3 Adjusted effects of feeding interval on outcomes

Variable	*Change in days (95% CI)*	P-*value*
Outcome: days to full feedings		
q3 feedings, vs q2	3.7 (1.6, 5.9)	0.001
Day of life feedings were started	−0.1 (−0.3, 0.02)	0.09
Days of trophic feedings	0.5 (0.1, 0.9)	0.005
Gestational age, per week older	−0.7 (−1.1, −0.3)	0.001
Center	1.1 (−0.8, 3.0)	0.24
	Odds Ratio (95% CI)	
Outcome: >28 days of TPN		
q3 feedings, vs q2	4.7 (1.5, 14.4)	0.008
Day of life feedings were started	1.2 (1.1, 1.3)	<0.001
Days of trophic feedings	1.4 (1.2, 1.6)	<0.001
Gestational age, per week older	0.7 (0.6, 0.9)	0.009
Center	0.8 (0.3, 2.1)	0.68
Outcome: ⩾7 days NPO		
q3 feedings, vs q2	4.7 (1.9, 11.7)	0.001
Day of life feedings were started	0.9 (0.9, 1.0)	0.09
Days of trophic feedings	1.3 (1.1, 1.5)	<0.001
Indomethacin therapy	3.9 (1.8, 8.3)	0.001
Mother's age, per 10 years older	0.5 (0.3, 0.8)	0.006
Gestational age, per week older	0.9 (0.7, 1.1)	0.20
Center	0.5 (0.2, 1.1)	0.10

Abbreviations: CI, confidence interval; NPO, nil per os; TPN, total parenteral nutrition. The table displays multivariable linear regression analysis of days to full feedings and logistic regression analyses of odds of receiving >28 days of TPN and of odds of having feedings held for ⩾7 days. The models included only the variables listed in the table.

In both bivariate and multivariable stratified analyses, the effect of feeding interval was greatest in the lower gestational age strata (Table 4), with infants born <28 weeks reaching full feedings 7.2 days (95% CI 1.5, 12.9 days) sooner on q2h feedings than on q3h feedings.

Secondary outcomes

Infants were re-categorized according to which regimen they were on at the start of the feeding advance, rather than which regimen they were on for the majority of the days. Nine infants were re-categorized: four infants started a q3 feeding advance but switched to continuous for feeding intolerance or residuals ($n = 2$) or after an episode of NEC ($n = 2$), one infant started on q2 but switched to continuous for residuals, and four infants started on q2 but switched to q3 after a period of NPO for residuals ($n = 1$), NEC ($n = 2$) or sepsis ($n = 1$). Crossovers during the period of trophic feedings or after reaching full feedings were not considered in this analysis. The result of a repeat analysis with the new categorization was similar to the primary analysis. In unadjusted and adjusted analyses, the q2 group reached full feedings 1.9 (95% CI 0.3, 3.6) and 2.0 (95% CI −0.4, 4.5) days more quickly than the q3 group.

We evaluated the duration of TPN and the total number of days feedings were held before the subjects reached full feedings. The models were constructed in the same manner as the primary outcome model. All variables included in the final models are listed in Table 3. The q3 group was more likely than the q2 group to have feedings held for at least 1 week (OR 4.7, 95% CI 1.9, 11.7) and more likely to receive more than 28 days of TPN (OR 4.7; 95% CI 1.5, 14.4).

Discussion

In a cohort of over 360 VLBW infants, we evaluated the impact of q2 versus q3 feeding interval on the time to reach full enteral feedings. When adjusted for potential confounding factors and center differences, we found that the q2 interval allowed infants to reach full feedings 3.7 days more quickly. Furthermore, q2 infants were less likely to receive prolonged TPN or have feedings held for more than a week. There are several possible explanations for our

Table 4 Difference in days to full feedings in q3 versus q2 groups, stratified by gestational age

Gestational age	*Unadjusted difference in days*	P-*value*	*Adjusted difference in days*	P-*value*
<28 weeks ($n = 108$)	5.3 (2.4, 8.1)	*<0.001*	7.2 (1.5, 12.9)	0.014
28 to $29^{6/7}$ weeks ($n = 117$)	3.6 (1.3, 5.8)	*0.002*	3.8 (−0.4, 6.8)	0.08
30 to $31^{6/7}$ weeks ($n = 91$)	2.1 (0.4, 3.9)	*0.019*	1.9 (−2.0, 5.8)	0.34
>32 weeks ($n = 46$)	−0.6 (−4.5, 3.3)	0.70	0.1 (−7.8, 8.0)	0.99

Values are reported as days (95% CI). Groups were compared with Student's *t*-test or multivariable linear regression adjusted for gestational age, day of life feeds began, days of trophic feedings and center.

findings. If feeding tolerance in VLBW infants is related to the volume of the feedings, the smaller volume q2 feedings should be better tolerated. Alternately, smaller volume feedings could lead to smaller *absolute* volume of residuals, and less frequent episodes of perceived 'feeding intolerance'.

The age at which patients reach both full-tube feeding and full-oral feeding is correlated with duration of hospitalization.[8] Despite the importance of safe, rapid achievement of full feedings, the literature contains little information about the influence of feeding interval on successful feeding. One small study by Rüdiger *et al*. evaluated the impact of different feeding intervals on time to full feedings and did not detect a difference between q2 and q3.[18] However, the median time to full feedings in that study was far longer than in the current study and other studies.[10] Furthermore, with fewer than 50 patients per group, the Rüdiger study was underpowered to detect a clinically important difference in time to full feedings.

Many aspects of the feeding regimens influenced the feeding outcomes in our study. The literature suggests that longer duration of trophic feedings promotes feeding tolerance.[1,3,7,8,23] Thus, in this study, the longer duration of trophics in the q2 group could have biased this group to a *shorter* time to full feedings. Alternately, a longer period of trophics could be a marker for severity of illness because each additional day of trophic feedings was associated with a 0.5-day increase in time to full feedings. Then, the q2 group would be expected to take a *longer* time to reach full feedings. When we accounted for duration of trophic feedings in multivariable analyses, the q2 group reached full feedings in significantly less time than the q3 group.

This study has several important strengths. This is the first study with sufficient power to confidently demonstrate the impact of different feeding intervals on clinically relevant endpoints. The cohort has a high proportion of eligible infants (362/378, 95.8%) included in the analysis. Finally, with the size of our population, we were able to adjust for many potentially confounding variables.

Our study is subject to the limitations of retrospective research. At our institutions, continuous feedings are reserved for cases of severe feeding intolerance. The strong selection bias for infants in the continuous feeding group led us to exclude these infants from further analyses. Baseline characteristics of the q2 and q3 groups were similar, but the q2 group was smaller and younger. This suggests that clinicians may have a bias when selecting feeding interval. Because smaller and younger infants have more difficulty tolerating feedings, this difference should bias the q2 group toward a longer time to full feedings, making our positive result more difficult to detect. Similarly, the lower rate of exclusive breast-milk feedings in the q2 group should have biased the group toward more feeding intolerance.[24] Although we adjusted our analyses for center, this is an observational study and differences between groups of infants, management styles of clinicians who prefer different feeding intervals, or the two hospitals could have resulted in unmeasured confounding. Infants were categorized according to an *a priori* definition of feeding interval, so an alternate definition of feeding interval might redistribute the crossovers and alter the results of the study. Finally, this study was not powered for stratified analysis or to detect the impact of feeding interval on outcomes such as length of stay or mortality.

This study suggests that the q2 feeding interval is associated with shorter time to full feedings in VLBW infants, with less feeding intolerance and requirement for TPN. In a larger sample, the shorter time to full feedings might result in shorter duration of hospitalization and reduction in morbidities such as central line infections. However, patient-related cost savings might be offset by increased nursing workload. This retrospective study is not sufficient evidence to warrant changes in clinical care. A prospective, randomized study of q2 versus q3 feeding intervals is necessary to confirm this result and bring neonatologists one step closer to understanding the safest and most efficient way to feed the VLBW infant.

Conflict of interest

The authors declare no conflict of interest.

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