Original Research Paper

A randomised controlled trial of high *vs* low volume initiation and rapid *vs* slow advancement of milk feeds in infants with birthweights ≤1000 g in a resource-limited setting

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Background: Optimal feeding regimens for infants ≤1000 g have not been established and are a global healthcare concern.

Aims and objectives: A controlled trial to establish the safety and efficacy of high *vs* low volume initiation and rapid *vs* slow advancement of milk feeds in a resource-limited setting was undertaken.

Methods: Infants ≤1000 g birthweight were randomised to one of four arms, either low (4 ml/kg/day) or high (24 ml/kg/day) initiation and either slow (24 ml/kg/day) or rapid (36 ml/kg/day) advancement of exclusive feeds of human milk (mother's or donor) until a weight of 1200 g was reached. After this point, formula was used to supplement insufficient mother's milk. The primary outcome was time to reach 1500 g.

Results: infants were recruited (51: low/slow; 47: low/rapid; 52: high/slow; 50: high/rapid). Infants on rapid advancement regimens reached 1500 g most rapidly (hazard ratio 1.48, 95% CI 1.05–2.09, $P=0.03$). The rapid advancement groups also regained birthweight more rapidly (hazard ratio 1.77, 95% CI 1.26–2.50, $P=0.001$). There was no apparent effect of high *vs* low initiation volumes but there was some evidence of interaction between interventions. There were no significant differences in other secondary outcomes, including necrotising enterocolitis, feed intolerance and late-onset sepsis.

Conclusions: In this small pilot study, higher initiation feed volumes and larger daily increments appeared to be well tolerated and resulted in more rapid early weight gain. These data provide justification for a larger study in resource-limited settings to address mortality, necrotising enterocolitis and other important outcomes.

Keywords: Infant preterm, Infant very low birthweight, Enteral nutrition, Necrotising enterocolitis

Introduction

The optimal feeding regimen for infants' born ≤1000 g has not been established. There is wide variation in enteral feeding practices worldwide, emphasising the need for evidence of efficacy and safety across all settings.[1] A delay in attaining full enteral nutrition is likely to compromise growth[2] and increase the risk of neurodevelopmental impairment.[3] However, disease severity, poor enteral tolerance, fear of necrotising enterocolitis (NEC) and aspiration, and ready availability of parenteral nutrition are all factors that have led to a conservative approach to initiating and advancing enteral feeds. This has now been challenged; a meta-analysis of randomised controlled trials[4] suggests that advancement of feeds in increments of up to 30–35 ml/kg/day does not increase the risk of NEC. However, some factors limit the application of these findings: sample sizes are small and extremely low birthweight infants are not well represented, comprising only around 10% of infants in studies to date. Rayyis *et al.*[5] excluded breastfed infants and only a third of participants in the study by Caple *et al.*[6] received human milk. Lango *et al.*[7] in our institution in South Africa demonstrated that early introduction of breast-milk feeding with minimal use of parenteral nutrition in extremely

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DOI 10.1179/2046905515Y.0000000056

low birthweight infants resulted in a mean growth velocity comparable with that achieved by infants receiving early parenteral nutrition and delayed enteral feeds. More rapid establishment of enteral feeds, especially of human milk, would reduce the risks of compromised nutrition and infection, and would be of particular value in a resource-limited setting with limited access to parenteral nutrition. In our institution, very low birthweight infants are eligible for full-time kangaroo mother care when they reach a weight of 1500 g. We therefore aimed to test the null hypothesis that in infants with birthweights $\leq$1000 g, high and low initiation and advancement volumes do not affect the rate at which a weight of 1500 g is attained.

Methods

The study was conducted in the tertiary level, neonatal unit at Groote Schuur Hospital in Cape Town, South Africa (trial registration ISRCTN96923718) and was approved by the Human Research Ethics Committee of the Faculty of Health Sciences in the University of Cape Town.

Design

The study design allowed separate assessment of the interventions, the higher starting volume and the faster advancement volume. Interactions between the interventions were also examined.

Outcome measures

The primary outcome was time to attain a weight of 1500 g. Secondary outcomes were time to regain birthweight, time to discharge, growth in head circumference from birth to discharge, growth in length from birth to discharge, mortality before discharge, incidence of NEC, any feed interruptions, any parenteral nutrition utilisation, and incidence of blood culture-confirmed late-onset sepsis.

Sample size

The sample size was calculated according to baseline data from Groote Schuur Hospital. Assuming equally sized groups and a 10% drop-out rate, we estimated that a total sample size of 200 infants would provide 80% power (at a significance level of 5%) to detect a hazard ratio of 1.7 for the primary outcome, time to attain a weight of 1500 g. The hazard ratio is the rate at which the 'event', in this case attainment of a weight of 1500 g, occurs in one group as the ratio to another group. The hazard can be thought of as an instantaneous probability of having the event in question. A hazard ratio is interpreted as follows: a hazard ratio of 2, for example, comparing rapid with slow advancement, would mean that, for infants who have not died, dropped out or reached the target weight, an infant in the rapid advancement group would be twice as likely to reach the target weight as an infant in the slow advancement group at any point in time. It was assumed that that was no interaction between interventions.

Trial procedures

Inborn infants with a birthweight of $\leq$1000 g were eligible for trial entry. Infants with congenital abnormalities which precluded enteral feeding or were immediately life-threatening were ineligible. Hypotension and inotropic support was not an exclusion criterion. Following informed, written parental consent, infants were randomly assigned to one of the following four groups: low volume initiation/slow advancement; low volume initiation/rapid advancement; high volume initiation/slow advancement; high volume initiation/rapid advancement.

Feeds were initiated on the day of birth with maternal expressed breast-milk (MEBM) or pasteurised donor expressed breast-milk (DEBM). Low volume initiation was 4 ml/kg/day and high volume initiation 24 ml/kg/day. Infants in the slow advancement groups received increments of 24 ml/kg/day and infants in the rapid advancement groups 36 ml/kg/day, until a volume of 200 ml/kg/day was reached.

Randomisation was performed using computer-generated allocation administered by telephone by an investigator who was off-site and blinded to the infant's clinical details at study entry other than gender and weight category. Thereafter, neither carers nor investigators were blinded to allocation group. Randomisation was performed stratified by gender and weight category ($<$700 g, 701–1000 g). Weight was chosen rather than gestational age because the latter information was not always reliably available.

Medical management

All infants received continuous nasogastric or orogastric feeds of exclusive human milk (MEBM/DEBM) until they weighed 1200 g. Breast-milk fortifier (BMF) (FM85® Nestlé nutrition) at a concentration of 1 g per 20 ml of breast-milk was added when an enteral feeding volume of 150 ml/kg/day was reached. At a weight of 1200 g, the infant was switched to 2-hourly bolus feeds by nasogastric or orogastric tube, and a pre-term formula, Similac Special Care® 20 (Abbott Nutrition), was used when MEBM was not available. Parenteral nutrition was initiated only when there was feeding intolerance exceeding 3 days or for confirmed cases of necrotising enterocolitis.

All infants received supplemental intravenous fluids until an enteral intake of 150 ml/kg/day was reached. All infants received caffeine 5 mg/kg/day, and, in cases of maternal human immunodeficiency virus, nevirapine 2 mg/kg/day. After enteral feeds of

150 ml/kg/day were reached and BMF commenced, the following supplements were added: 0.3 ml oral multivitamins (kiddy-vit®, Barra Pharmaceutical) daily; 0.5 mmol oral sodium chloride 6-hourly; infants who were ≤32 weeks gestation at birth were also given 0.5 mmol/kg/day of oral phosphate; the phosphate dose was titrated according to the phosphate levels. Oral ferrous lactate 0.2 ml (6 mg/kg/day elemental iron) daily was added from postnatal day 21.

Infants were weighed daily; lengths and head circumferences were measured weekly and these measurements were plotted on a Fenton growth chart.[8]

Indications to suspend feeds were tense abdominal distension, erythema of the abdominal wall, decreased bowel sounds, gross or occult blood in the stool, abdominal tenderness, bile-stained gastric aspirates, pneumatosis intestinalis or vomiting after two consecutive feeds, despite correct position of the nasogastric or orogastric tube. Clinical suspicion of NEC was categorised according to Bell's staging criteria.[9] Only infants with signs consistent with Bell stage II or III were included in the NEC outcome. Infants who were kept nil by mouth after presenting only with abdominal distension and who subsequently had a normal abdominal examination within 24 hours had their feeds recommenced at the volume they had previously reached; feeds were subsequently advanced according to their group assignment.

Data analysis

Data were analysed using Stata version 12 (Stata Corporation, College Station, USA). Analyses were undertaken on an intention-to-treat basis. Statistical significance was set at $P=0.05$. For each of the time-to-event outcomes (attainment of 1500 g weight, re-attainment of birthweight and length of stay), Kaplan–Meier survival curves were used to compare treatment groups (low volume initiation *vs* high volume initiation, and slow advancement *vs* rapid advancement). Cox regression models were used to estimate hazard ratios and associated 95% confidence intervals comparing groups. Plots and tests of Schoenfeld residuals were used to check the proportional hazards assumption. If hazards were non-proportional, the hazards were estimated separately for two intervals by splitting the data according to median survival time.[10] The proportional hazards assumption was checked again after splitting the time period. Interaction between the interventions (i.e. the effect of low and high volume initiation on outcomes according to speed of advancement) was tested, although the study was underpowered to detect treatment effects in the presence of an interaction. Hazard ratios were estimated in models with and without inclusion of the interaction term. For weight attainment outcomes, patients were censored if they died before attaining the weight. Log rank tests and Cox regressions were stratified in accordance with randomisation strata.

The binary outcomes NEC, mortality, blood culture-confirmed late-onset sepsis, feed interruptions and parenteral nutrition utilisation were analysed using logistic regression, adjusting for randomisation strata. Differences between groups are presented as odds ratios and associated confidence intervals. Growth in head circumference and length between birth and discharge were calculated for infants who were discharged home. Data were log-transformed owing to skewness before analysis using linear regression, adjusting for randomisation strata. Differences between treatment groups are presented as the percentage difference and associated confidence intervals.

Results

During the enrolment period, August 2011 to February 2013, 214 infants with a birthweight ≤1000 g were admitted to the neonatal unit and 200 infants were recruited. The flow of recruitment, reasons for exclusion and group totals are shown in Fig. 1. Feeds were initiated within the first 24 hours in all patients. Hypotension and inotropic support affected only one infant. Baseline demographic and clinical characteristics were similar in the four groups (Table 1).

Primary outcome: time to attain 1500 g

Fig. 2-4 shows the Kaplan–Meier plot for time to attain 1500 g. Results of the Cox regression models are shown in Table 2. Examining the interventions separately, infants receiving rapid advancement of enteral feeds were more likely to reach a weight of 1500 g before infants receiving slow advancement (model 1 hazard ratio 1.48, 95% CI 1.05–2.09, $P=0.03$). There was no significant effect of high *vs* low initiation volumes (model 1 hazard ratio 1.05, 95% CI 0.75–1.50, $P=0.75$). There was evidence of an interaction between the interventions ($P=0.02$). When the interaction was included, infants on the high volume initiation and rapid advancement feeding schedule were more likely to reach 1500 g earlier than the low volume initiation and slow advancement group (model 2 hazard ratio 1.62, 95% CI 1.01–2.59, $P=0.05$). As there was evidence of non-proportional hazards ($P=0.01$), data were split at median time to attain a weight of 1500 g (47 days). In the first 47 days, infants in the high and rapid group were more likely to reach 1500 g earlier than the low and slow group (model 3 hazard ratio 2.29, 95% CI 1.32–3.97, $P=0.003$) but the effect was lost after 47 days (model 3 hazard ratio 0.91, 95% CI 0.46–1.77, $P=0.77$).

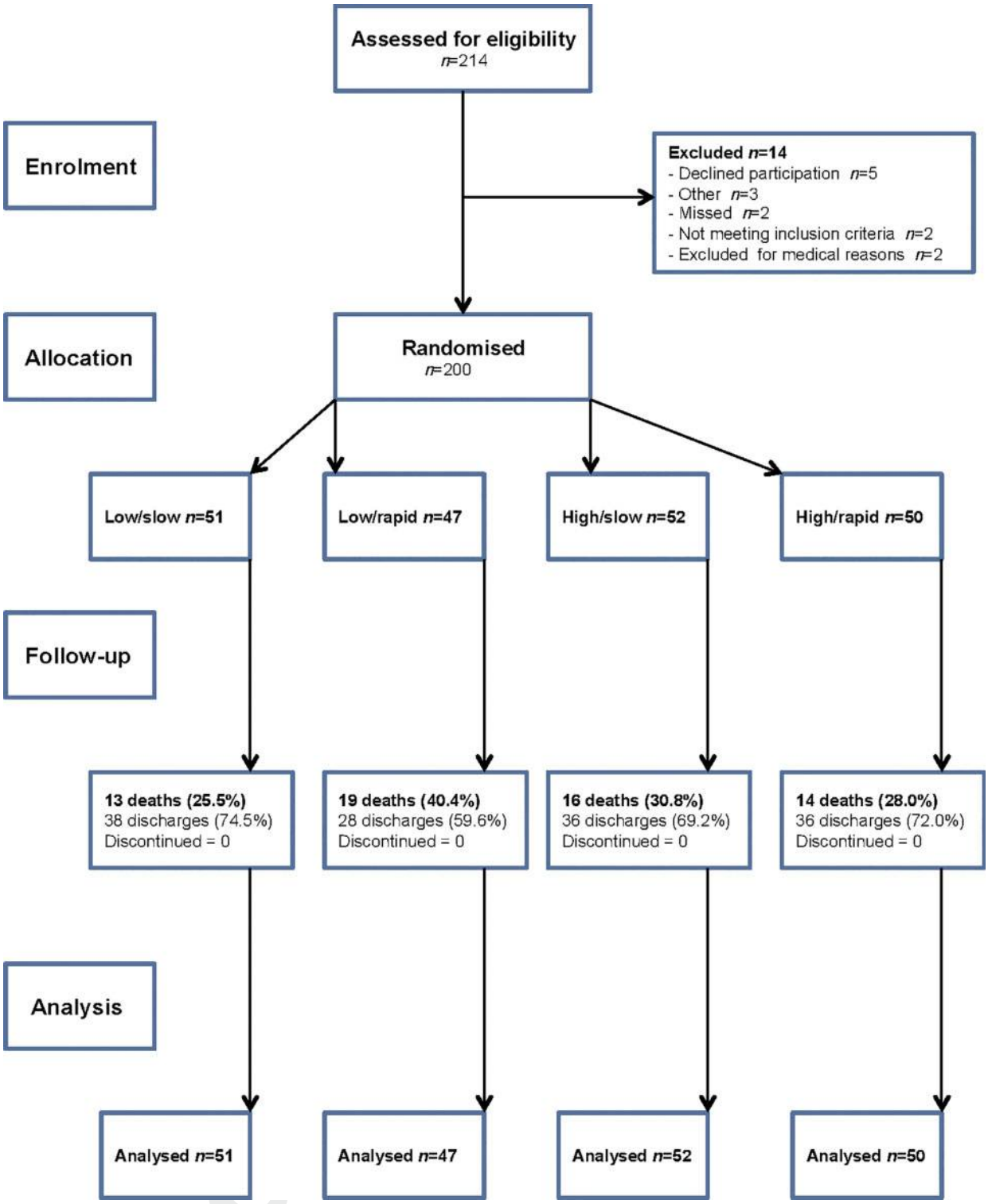

Figure 1 Flowchart of study patients

Secondary outcomes: time to regain birthweight and time to discharge

The hazard ratios for these outcomes are shown in Table 3. Infants receiving rapid advancement were more likely to regain birthweight earlier than those on the slow advancement schedule (model 1 hazard ratio 1.77, 95% CI 1.26–2.50, $P=0.001$). There was no significant effect of high *vs* low initiation volumes (model 1 hazard ratio 1.17, 95% CI 0.84–1.63, $P=0.35$). There was no evidence of interaction between the interventions but there was evidence of non-proportional hazards ($P=0.04$), so data were split according to median time to regain birthweight (13 days). This showed that in the first 13 days infants receiving rapid advancement were more likely to regain their birthweight earlier than infants on the slow advancement regimen (model 3 hazard ratio 2.26, 95% CI 1.42–3.60, $P=0.001$); this effect was not statistically significant after 13 days (model 3 hazard ratio 1.29, 95% CI 0.75–2.21, $P=0.37$).

Table 1 Patient characteristics*

Demographic variables	Low/slow Total = 51 *n* (%)†	Low/rapid Total = 47 *n* (%)†	High/slow Total = 52 *n* (%)†	High/rapid Total = 50 *n* (%)†
Pregnancy induced hypertension	29 (57.0)	32 (68.0)	35 (67.0)	40 (80.0)
Multiple pregnancy				
Twins	4 (7.8)	7 (15.0)	4 (7.7)	4 (8.0)
Triplets	2 (3.9)	0	0	0
Onset of labour:				
Spontaneous	11 (21.6)	9 (19.1)	12 (23.0)	8 (16.0)
Unmonitored induction	2 (3.9)	2 (4.3)	2 (3.8)	3 (6.0)
Caesarean section	38 (74.5)	36 (76.6)	38 (73.1)	39 (78.0)
Gestation at delivery:				
Mean (SD)	28.7 (1.6)	28.9 (2.5)	29.0 (1.9)	29.1 (2.0)
< 29 weeks	26 (51.0)	26 (55.0)	20 (38.5)	21 (42.0)
≥ 29 weeks	25 (49.0)	21 (45.0)	32 (61.5)	29 (58.0)
Male	22 (43.1)	21 (44.7)	20 (38.5)	23 (46.0)
Birthweight, g:				
Mean (SD)	845 (114.5)	858.5 (105.0)	833 (95.0)	853.5 (116.0)
< 600 g	1 (2.0)	0	1 (1.9)	1 (2.0)
600–749 g	9 (17.6)	8 (17.0)	9 (17.3)	12 (24.0)
750–1000 g	41 (80.4)	39 (83.0)	42 (80.8)	37 (74.0)
Mean 1-min Apgar (SD)	5.6 (2.9)	5.5 (2.5)	5.4 (2.7)	5.9 (2.7)
Mean 5-min Apgar (SD)	7.5 (2.6)	7.6 (2.1)	7.5 (1.9)	7.9 (2.1)
Positive pressure ventilation	7 (13.7)	2 (4.3)	4 (7.7)	1 (2.0)
Nasal continuous airway pressure	39 (76.5)	38 (80.9)	46 (88.5)	43 (86.0)
Maternal HIV	9 (17.6)	13 (27.6)	13 (25.0)	12 (24.0)
Antenatal corticosteroids	32 (62.7)	31 (66.0)	31 (59.6)	26 (52.0)
Intrauterine growth restriction	32 (62.7)	29 (61.7)	37 (71.2)	35 (70.0)

* There was no statistically significant difference between the groups; † unless otherwise specified; HIV: human immunodeficiency virus; SD: standard deviation

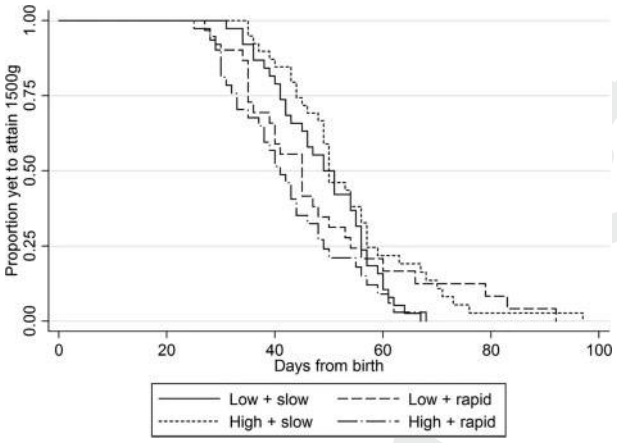

Figure 2A Proportion yet to attain 1500 g body weight by age in days (4 groups)

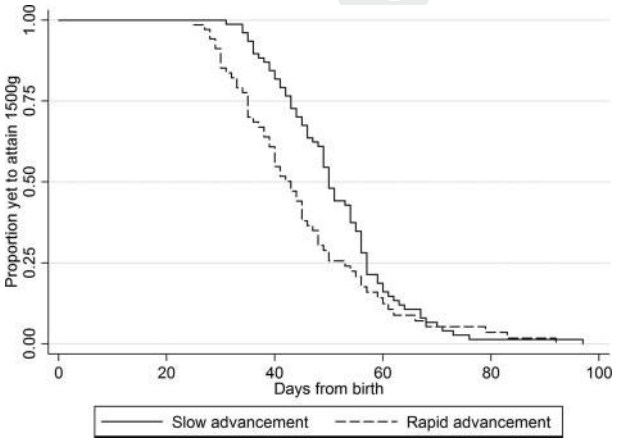

Figure 2B Proportion yet to attain 1500 g body weight by age in days (slow *vs* rapid advancement of feeds)

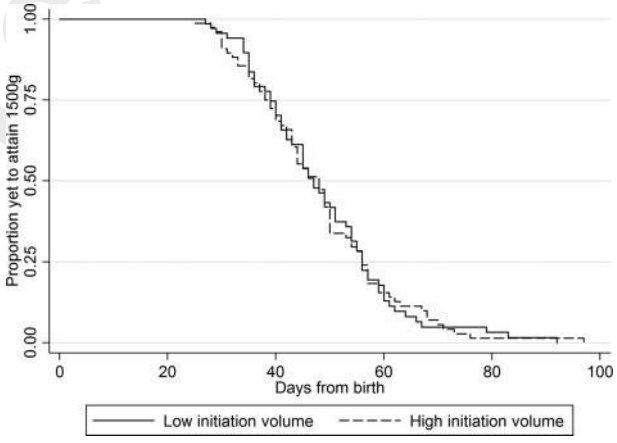

Figure 2C Proportion yet to attain 1500 g body weight by age in days (low *vs* high initiation volume)

There was no significant effect of either high initiation volume or rapid advancement of feeds on time to discharge when examining the interventions separately. As there was evidence of an interaction between the interventions (P=0.049) and of non-proportional hazards (P=0.05), the data were split according to median time to discharge (58 days). High initiation volume and rapid advancement of feeds was associated with earlier discharge (model 4 hazard ratio 1.77, 95% CI 1.03–3.03, P=0.04) but this effect was not significant after 58 days (model 4 hazard ratio 0.81, 95% CI 0.42–1.57, P=0.53).

Odds ratios and absolute data for mortality and morbidity are shown in Tables 4 and 5, respectively. A treatment interaction was not tested for NEC as

Table 2 Primary outcome: time to attain 1500 g

Study group	Hazard ratio	*P*-value	95% CI
Model 1: Without interaction			
High *vs* Low	1.05	0.75	0.75–1.50
Rapid *vs* Slow	1.48	0.03	1.05–2.09
Model 2: With interaction*			
High/slow *vs* Low/slow	0.73	0.19	0.46–1.16
Low/rapid *vs* Low/slow	0.96	0.86	0.57–1.59
High/rapid *vs* Low/slow	1.62	0.05	1.01–2.59
Model 3: Split time period with interaction†			
High/slow *vs* Low/slow (whole time period)	0.70	0.14	0.43–1.12
Low/rapid *vs* Low/slow (before 47 days)	1.48	0.21	0.80–2.73
Low/rapid *vs* Low/slow (after 47 days)	0.59	0.11	0.31–1.12
High/rapid *vs* Low/slow (before 47 days)	2.29	0.003	1.32–3.97
High/rapid *vs* Low/slow (after 47 days)	0.91	0.77	0.46–1.77

* Interaction (P=0.02), (the effect of low vs. high volume initiation varies with rate of advancement); † split time period ($P = 0.01$), (hazard ratios for the effect of rapid advancement was not constant over time, hence data were split at median time to attain a weight of 1500 g (47 days)

Table 3 Secondary outcomes: time to regain birth weight and time to discharge

Study group	Hazard ratio	*P*-value	95% CI
Time to regain birthweight			
Model 1: Without interaction			
High *vs* Low	1.17	0.35	0.84–1.63
Rapid *vs* Slow	1.77	0.001	1.26–2.50
Model 2:With interaction*			
High/slow *vs* Low/slow	1.02	0.93	0.65–1.60
Low/rapid *vs* Low/slow	1.52	0.09	0.93–2.48
High/rapid *vs* Low/slow	1.35	0.38	0.70–2.60
Model 3: Split time period without interaction†			
High *vs* Low	1.16	0.38	0.83–1.61
Rapid *vs* Slow (before 13 days)	2.26	0.001	1.42–3.60
Rapid *vs* Slow (after 13 days)	1.29	0.37	0.75–2.21
Time to discharge			
Model 1: Without interaction			
High *vs* Low	0.96	0.80	0.69–1.35
Rapid *vs* Slow	1.37	0.08	0.97–1.93
Model 2: With interaction‡			
High/slow *vs* Low/slow	0.69	0.12	0.43–1.10
Low/rapid *vs* Low/slow	0.94	0.82	0.57–1.57
High/rapid *vs* Low/slow	1.33	0.23	0.83–2.11
Model 3: Split time period without interaction			
High *vs* Low	0.91	0.60	0.65–1.29
Rapid *vs* Slow (before 58 days)	1.92	0.006	1.21–3.05
Rapid *vs* Slow (after 58 days)	0.86	0.60	0.49–1.49
Model 4: Split time period with interactionï			
High/slow *vs* Low/slow (whole time period)	0.66	0.09	0.41–1.07
Low/rapid *vs* Low/slow (before 58 days)	1.34	0.33	0.74–2.45
Low/rapid *vs* Low/slow (after 58 days)	0.62	0.14	0.32–1.18
High/rapid *vs* Low/slow (before 58 days)	1.77	0.04	1.03–3.03
High/rapid *vs* Low/slow (after 58 days)	0.81	0.53	0.42–1.57

* Interaction non-significant (the effect of low *vs* high volume initiation varies with rate of advancement); † split time period ($P = 0.04$) (hazard ratios for the effect of rapid advancement were not constant over time, hence data were split at the median time to regain birth weight – 13 days); ‡ interaction $P = 0.049$ (the effect of low *vs* high volume initiation varies with rate of advancement); ï split time period ($P = 0.05$) (hazard ratios for the effect of rapid advancement were not constant over time, hence data were split at the median time to discharge – 58 days)

numbers were small; there was no evidence of a treatment interaction for other outcomes. No significant differences were identified between the groups. Overall mortality to discharge was 31%; 9.5% of infants developed NEC and 16% late onset sepsis.

Discussion

In this pragmatic, randomised controlled trial conducted in a low-resource setting, it is shown that higher initiation feed volumes and larger daily increments appear to be well tolerated by infants of $\leq$1000 g birthweight. More rapid advancement resulted in more rapid rates of achieving a weight of 1500 g, regaining birthweight and discharge. Mortality and feed-related morbidity including NEC were not increased, though it is acknowledged that the study was underpowered to assess these outcomes. The impact of time-to-event outcomes decreased with

Table 4 Secondary outcomes: odds ratios for morbidity and mortality

	Odds ratio*	P value	95% CI
Necrotising enterocolitis			
High *vs* Low	1.35	0.54	0.51–3.57
Rapid *vs* Slow	1.00	0.99	0.38–2.64
Mortality			
High *vs* Low	0.85	0.60	0.46–1.60
Rapid *vs* Slow	1.33	0.40	0.72–2.50
Feed interruptions			
High *vs* Low	1.10	0.74	0.63–1.94
Rapid *vs* Slow	0.86	0.60	0.50–1.50
Parenteral nutrition			
High *vs* Low	0.80	0.60	0.32–1.83
Rapid *vs* Slow	0.76	0.50	0.32–1.82
Late-onset sepsis			
High *vs* Low	0.70	0.40	0.32–1.50
Rapid *vs* Slow	0.70	0.30	0.32–1.50
Head growth†			
High *vs* Low	−1.7†	0.84	−16.7–16.1
Rapid *vs* Slow	2.2†	0.80	−13.6–1.21
Length growth†			
High *vs* Low	0.16†	0.84	0.18–0.15
Rapid *vs* Slow	0.22†	0.80	0.15–0.20

* Unless otherwise specified; † percentage difference from birth to discharge between groups

time, suggesting that most benefit may be obtained where early discharge and/or weight-dependent kangaroo mother care are practiced. The findings are particularly relevant to low-resource settings where parenteral nutrition is not readily available.

The strengths of the study include the rigorous design, delivered in a real-world resource-limited setting. The hazard ratio was used to compare time-to-event outcomes between groups using regression analysis (in this case Cox regression), retaining data from infants who dropped out or died. This is important, given the high mortality rate in this population.

As far as we are aware, this is the only study to date to examine both the volume of initiation and the volume of advancement. Importantly, infants with birthweights $\leq$1000 g were enrolled, a previously under-represented but extremely vulnerable group. All infants received exclusive feeds of human milk until they weighed 1200 g, and it would be inappropriate to extrapolate the findings to infants fed with formula as this could lead to differences in enteral tolerance. Of note is that approximately two-thirds of the study population were growth-restricted and, as this is an independent risk factor for NEC, it is reassuring that no differences in this outcome between the groups were identified.

An important limitation of the study it that it was not powered to detect clinically relevant differences in NEC, mortality and late-onset sepsis. Additionally, the nature of the interventions precluded blinding; the clinicians who reviewed abdominal radiographs were not blinded to group allocation and it was not possible to follow infants after discharge; hence, any later effects of more rapid early weight gain are not known.

The data accord with and extend the findings of previous randomised controlled trials and Cochrane meta-analyses. These conclude that volumes of feed advancement up to 30–35 ml/kg/day[4] or introduction of progressive enteral feeds in the first 4 days after birth[11] do not increase the risk of developing NEC in very preterm, very low birthweight or growth-restricted infants. The data in this study add to the accumulating evidence that immediate introduction of milk feeds is safe and improves outcomes in preterm and extremely low birthweight infants. A randomised controlled trial (SIFT, NCT01727609) in which fast (30 ml/kg/day) *vs* slow (18 ml/kg/day) advancement of feeds are compared is currently recruiting subjects in the UK and will provide important data, particularly of relevance to high-income countries, including evaluation of outcomes at 2 years of age.

Preterm and low-birthweight rates are rising worldwide and the optimum care of these infants in resource-limited settings requires a sound evidence-base. The stratagem evaluated in this study is potentially an important advance in the care of these vulnerable infants. The finding that higher feed initiation and advancement of volumes appear safe and well tolerated in this small pilot study is justification to proceed to larger studies powered to address mortality and a range of important short-term morbidities, principally NEC, as well as longer-term outcomes.

Table 5 Outcomes (raw data)

Outcomes	Overall Total = 200 *n* (%)	Low/slow Total = 51 *n* (%)	Low/rapid Total = 47 *n* (%)	High/slow Total = 52 *n* (%)	High/rapid Total = 50 *n* (%)
Days to attain 1500 g, median (IQR)	46.5 (39–56)	50.0 (41–56)	45.0 (35–53.5)	50.0 (44.5–57)	40.5 (32.5–48.5)
Days to regain birthweight, mean (SD)	13.6 (4.21)	14.9 (4.18)	12.7 (4.48)	14.9 (4.31)	11.8 (3.02)
Days to discharge, median (IQR)	58 (46–68)	59.0 (49–67)	50.5 (42.5–67)	61.0 (56.5–70.5)	53.0 (44.5–66)
Infants developing NEC	19 (9.5)	1 (2.0)	7 (15)	9 (17)	2 (4)
Deaths to discharge	62 (31.0)	13 (25.5)	19 (40.4)	16 (30.8)	14 (28.0)
Infants with feed interruptions	82 (41)	20 (39.2)	19 (40.4)	24 (46.2)	19 (38)
Infants requiring parenteral nutrition	24 (12)	6 (11.8)	7 (14.9)	8 (15.4)	3 (6.0)
Infants with late-onset sepsis	32 (16)	9 (17.6)	9 (19.1)	10 (19.2)	4 (8.0)

NEC, necrotising enterocolitis; IQR, Interquartile range (25–75th percentile)

Disclaimer statements

Contributors M Shukri Raban: As the principal investigator, Dr Raban conceptualized and designed the study, drafted the initial manuscript and approved the final manuscript as submitted. Shalini Santhakumaran: Ms Santhakumaran assisted in the design of the study, particularly the analysis plan, assisted with the initial data analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.Quanitah Keraan and Yaseen Joolay: Drs. Keraan and Joolay coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. Alan Horn, Neena Modi and Michael Harrison: Professors Modi, Horn and Harrison assisted in the design of the study, assisted with the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.

Funding No.

Conflict of interest The authors have no conflicts of interest relevant to this study to disclose Grants In the last five years NM has held research grants awarded by the National Institute of Health Research, Welcome Trust, Acton Medical Research, Child Growth Foundation, Department of Health, Westminster Medical School Research Trust, Healthcare Quality Improvement Partnership, HCA International, and Bliss. SU has held a research grants from the National Institute of Health Research.

Ethics approval Study approved by University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee.

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