[haematologica reports]
2006;2(10):80-85

Update on the SAFEstart Clinical Trials

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A B S T R A C T

Certain growth factors exist in relatively high concentrations in fluids swallowed by the fetus and neonate; namely amniotic fluid, colostrum, and human milk. We postulated that; 1) after these factors are swallowed they are not enterally digested into non-functional units, but remain biologically active, 2) the ingested factors bind to specific receptors on the luminal surface of villous enterocytes where they exert a topical antiapoptotic effect, 3) the ingested factors are not absorbed into the blood and have no systemic effect, 4) when a fetus is delivered prematurely and amniotic fluid swallowing abruptly ceases, if the patient is NPO (thus receiving no growth factors from colostrum or milk) disuse atrophy of the small bowel mucosa can begin, leading to feeing intolerance once milk feedings are started. We developed a sterile, isotonic, growth factor-containing solution, simulating second trimester amniotic fluid. We called the fluid SAFEstart® (an acronym for Simulated, Amniotic Fluid for Enteral administration); a patent was obtained by the University of Florida. The growth factors contained in SAFEstart were concentrated 10 fold above natural amniotic fluid, so that 20 mL/k/d of SAFEstart would provide the amount of growth factors ingested by a fetus swallowing 200 mL/k/d of amniotic fluid. Preclinical studies on stability and digestion were followed by six clinical trials. Whether mixed with human milk, preterm infant formulas, or kept by itself, SAFEstart was stable for at least three weeks frozen, with only minimal and gradual degradation of activity in the weeks thereafter. No evidence of absorption of factors into the blood and no systemic effects were observed after usage. Four clinical trials have examined its use to prevent feeding intolerance and two additional trials have examined its treatment use among neonates with established feeding intolerance. CONCLUSIONS: One hundred-twenty neonates have now participated in six SAFEstart trials. It is feasible to administer 20 mL/k/d of SAFEstart (2.5 mL/k every 3 h) to ill preterm neonates, and it is well tolerated, with no safety issues uncovered to date. Early controlled studies suggest efficacy in preventing feeding intolerance and also in treating established feeding intolerance, presumably by topical actions of relevant growth factors on the small bowel mucosa. Multicentered randomized, placebo controlled trials are now needed to estimate the risks and benefits of administering SAFEstart to neonates who are otherwise NPO.

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Feeding intolerance in the NICU can present as distended loops of bowel, emesis, large pre-feeding gastric residuals, diarrhea, or gross blood in the stools.[1] These problems can prolong the need for parenteral nutrition and add to the length of the hospitalization.[2] Disuse atrophy of the small bowel mucosa, following several days of enteral fasting, is one factor that can contribute to, or delay recovery from, feeding intolerance among NICU patients.[3] We conducted a series of basic and clinical studies aimed at reducing feeding intolerance by enterally administering a sterile, isotonic, non-caloric, growth factor-containing solution patterned after human amniotic fluid.[4] The experimental solution we devised has the electrolyte composition of amniotic fluid and contains albumin and two enterocyte growth factors present in human amniotic fluid, colostrum, and human milk; namely recombinant erythropoietin (rEpo) and recombinant granulocyte-colony stimulating factor (rG-CSF).[5]

We previously showed that this solution is stable,[5] and that the growth factors in it are relatively resistant to digestion.[6] We also reported that the cognate receptors for these growth factors are expressed on the luminal surface of fetal intestinal villi[7,8] and when ingested by neonates these factors are not detected in the blood and have no hematopoietic effects.[9,10]

Our previous phase I clinical trials using this solution suggested it is well tolerated when administered at a dose of 20 mL/kg/day (2.5 mL/kg every 3 hours).[4,11-14] No randomized, controlled trials have previously been done testing this solution, yet

such studies are essential to determining whether it is effective in preventing or treating feeding intolerance. The present study was designed as a small, randomized, controlled, masked trial, to obtain preliminary information needed to design a phase III efficacy trial. Specifically, we studied twenty NICU patients who had manifestations of feeding intolerance, randomizing them to either receive the test solution at a dose of 20 mL/kg/day for up to seven days, or to sham administrations. The researchers and caregivers, except the bedside nurse who actually administered the doses or gave the sham administrations, did not know the randomization group. The outcome measures were the daily enteral calories received for the period the test solution (or sham administration) was given and for the seven-day period after it was discontinued.

Methods

Patients

Subjects were eligible for study if they had the diagnosis of feeding intolerance as defined below. Patients were excluded from consideration if they had a congenital surgical condition involving the gastrointestinal tract such as tracheoesophageal fistulae, diaphragmatic hernia, Hirschsprung's disease, bowel atresia, gastroschesis, or omphalocele or if they were judged as being too ill to enroll in this study, as defined by a requirement for mechanical ventilation with >50% FIO_2. Feeding intolerance was defined, for the purpose of the study, as the presence on at least three consecutive days of any of the following that thwarted the written enteral feeding plan; increased abdominal girth, emesis, gastric residuals in excess of 1 feeding, diarrhea, visible blood in the stool not otherwise explained, or abnormally large bowel loops on physical examination or abdominal radiograph. The Intermountain Healthcare Institutional Review Board approved the protocol and parent's informed consent was obtained.

Study procedures

The hospital pharmacist produced the experimental solution using sterile technique and the parenteral nutrition equipment in the manner previously reported.5 The solution contained 115 meq/L sodium chloride, 17 meq/L sodium acetate, 4 meq/L potassium chloride, 225 ng/mL rG-CSF (Neupogen, Filgrastim, Amgen Inc, Thousand Oaks, Ca. USA) and 4400 mU/mL rEpo (Epoetin alfa, Epogen, Amgen). Human serum albumin (Baxter Health Care Corp, Hyland Division, Glendale, Calif) was added to the infusion bag prior to adding the cytokines (the final concentration of albumin was 0.05%). A patent for this solution is held by the University of Florida (U.S. Patent No. 6956023).

Randomization was performed by the hospital pharmacy department using a random number table. On each day a patient was on study, the pharmacist would sent to the NICU either a full day's dose of test solution (eight syringes, each containing 2.5 mL/kg) or eight empty syringes. The syringes were covered in pharmacy bags to mask the contents from all except the bedside nurse. The syringes were refrigerated until use. Before administration, a syringe was placed near the patient in the incubator for 10 to 15 minutes to increase the temperature before it was administered through the oral-gastric tube. Once milk feedings were ordered, the experimental solution was mixed with the milk. The test solution (or sham treatment) was discontinued when the enteral intake reached 80 mL/kg of milk, or after a maximum of seven days.

Measurement of enteral caloric intake

The volume of milk feeding for each patient was recorded daily, beginning three days before the test solution (or sham administration) was initiated and ending seven days after it was discontinued. The estimated volume of any emesis recorded by the bedside nurse, and the estimated volume of any gastric residual that was not returned to the patients, were subtracted from the enteral intake in order to calculate net milk intake per day. For consistency, unfortified human milk was calculated as containing 0.67 cal/mL (20 cal/oz), or 0.74 cal/mL (22 cal/oz) or 0.8 cal/mL (24 cal/oz) when fortified with human milk fortifier (Similac® Human Milk Fortifier, Ross Pediatrics, Columbus, Ohio, or Enfamil® Human Milk Fortifier, Mead Johnson & Company, Evansville, Indiana) was added according to manufactures instructions.

Statistical analysis

The purpose of the study was to determine the enteral calories taken during the period the test solution (or sham administration) was given, and again during the seven-day period after the test solution (or sham administration) had been stopped. Calculations of net enteral calories were expressed as calories/kg body weight/day. Because the outcome of interest (calories/kg/day) was not parametrically distributed, the values were expressed both as median and range. For continuous variables with normal distribution, means and standard deviations were used. For comparison of enteral calories taken by the test vs. control group and estimates for powering a phase III efficacy trial, independent samples t-tests with unequal variances assumptions were used. A Fisher's Exact test was used to assess differences in categorical variables. All analyses were one-sided with $p < 0.05$ taken as significant.

Table 1. NICU patients who had feeding intolerance and were randomized to receive sham administrations (control group).

Patient number	*Birth wt (g)*	*Gest Age (w)*	*Feeding intolerance manifestations and associations*
1	1392	29 1/7	Increased abdominal girth and visible bowel loops. KUB showed dilated loops and thickened bowel wall but no definite pneumatosis. Occurred while on Enfamil premature formula (22 cal/oz), 30 mL every three hr. Antibiotics started.
2	2529	35 5/7	Grossly bloody stools. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on BM and Similac 22 (when BM not available) 52 mL every three hr. Andersen tube placed, antibiotics started.
3	683	24 4/7	Diarrhea. Thought to be viral gastroenteritis with concomitant respiratory deterioration. Occurred while on BM 16 mL every three hrs.
4	2139	34 2/7	Grossly bloody stools. Occurred while on BM (22 cal/oz) every 3 hrs. Andersen tube placed, antibiotics started.
5	1096	30 0/7	Increased abdominal girth, diarrhea, visible bowel loops, grossly blood stools. Occurred while on Enfamil premature formula (22 cal/oz), 11 mL/hr (continuous).
6	1152	27 2/7	Increased abdominal girth and bilious emesis. KUB showed no definite pneumatosis. Occurred while on BM and Similac NeoSure (22 cal/oz) 10 mL every three hr. Andersen tube placed and antibiotics started.
7	3209	37 5/7	Grossly bloody stools. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on BM (22 cal/oz) 23 mL every 3 hr. Andersen tube placed, antibiotics started.
8	1110	31 2/7	Increased abdominal girth and mucous in stools. KUB showed no definite pneumatosis. Occurred while on BM (22 cal/oz). Andersen tube placed, antibiotics started.
9	2676	36 5/7	Increased abdominal girth and bilious emesis. KUB showed no definite pneumatosis. Occurred while on BM feedings, po, ad lib. Andersen tube placed and antibiotics started.
Mean ±SD	1776 ±880	31.6 ±4.4	

wt = weight; gest = gestational; g=grams; w=weeks; KUB = abdominal radiograph (kidney, ureters, bladder); BM = breast milk

Results

During the months of July 2005 through April 2006, the families of 23 eligible NICU patients were contacted to inquire whether they were interested in learning about the feeding tolerance study. Twenty of the 23 families gave written consent for their neonate to participate in the study, and three did not. All 20 where consent was given were enrolled in the study and none were withdrawn from the study after enrolling. No otherwise eligible patients were excluded from the study on the basis that they were judged as being too ill to enroll in the study. The 20 subjects were a heterogeneous group, with birth weights ranging from 403 to 4093 grams, and gestational ages ranging from 25 to 39 weeks. The signs of feeding intolerance in each of the 20 subjects are shown in Table 1 (sham recipients) and Table 2 (test solution recipients).

Fourteen of the 20 subjects had feeding intolerance while receiving human milk feedings exclusively. Seven of these 14 were receiving unfortified human milk, while seven were receiving human milk fortified to a calculated content of 22 cal/oz (five subjects), or 24 cal/oz (two subjects). Three of the 20 subjects had feeding intolerance while receiving a combination of human milk and infant formula. Two of the twenty had feeding intolerance while exclusively feeding with Enfamil Premature Formula (22 cal/oz, Mead Johnson & Company, Evansville, Indiana) and one while exclusively feeding with Enfamil (20 cal/oz).

At the time the test solution (or sham administration) was started, and each day it was given, all twenty patients were receiving parenteral nutrition, including amino acids, electrolytes, trace minerals, vitamins, and lipids. None of the study patients had a recognized adverse reaction to the test solution. Specifically, none developed a rash, hypotension, or worsening of respiratory distress, or worsening of feeding intolerance during the days the test solution was given.

All decisions regarding when to begin milk feedings, and how rapidly to advance the volumes of those feedings, were made on a daily basis by the attending neonatologist and neonatal nurse practitioner. The test solution was given for as few as two days and for as many as seven days.

During the 72 hr period preceding administration of the test solution, most of the subjects were receiving no enteral intake, with a range from 0 to 33 cal/k/d for that 72 hr period (Table 3). During the days the

Table 2. NICU patients who had feeding intolerance and were randomized to receive the test solution.

Patient number	*Birth wt (g)*	*Gest Age (w)*	*Feeding intolerance manifestations and associations*
1	934	29 3/7	Visible bowel loops, increased abdominal girth, large prefeeding-gastric residuals. Occurred while on BM 1.5 mL every 3 hrs.
2	403	25 1/7	Increased abdominal girth, bluish discoloration to abdomen. Occurred while on BM 1.5 mL every 3 hrs.
3	4093	39 0/7	Grossly blood stools. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on Enfamil (20 cal/oz) 75 mL every 3 hrs. Andersen tube placed, antibiotics started.
4	704	29 3/7	Increased abdominal girth, increased 2 cm, full and tender abdominal examination. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on BM (22 cal/oz) 11 mL every 3 hrs. Andersen tube placed, antibiotics started.
5	1584	30 5/7	Emesis, diarrhea, increased abdominal girth, visible bowel loops, grossly bloody stools. Occurred while on BM 11 mL/hr (continuous). Andersen tube placed, antibiotics started.
6	1328	27 6/7	Increased abdominal girth Occurred while on BM 12 mL every 3 hrs.
7	1250	36 5/7	Increased abdominal girth, visible bowel loops, increased girth by 4 cm. KUB showed no definite pneumatosis. Occurred while on BM (24 cal/oz) 26 mL every 3 hrs. Andersen tube placed, antibiotics started.
8	2331	32 6/7	Grossly blood stools. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on BM (22 cal/oz) and Enfamil Premature (22 cal/oz) 32 mL every 3 hrs. Andersen tube placed, antibiotics started.
9	1318	32 6/7	Grossly blood stools and increased abdominal girth.. KUB showed pneumatosis. Rotavirus positive stools. Occurred while on BM (24 cal/oz) 30 mL every 3 hrs. Andersen tube placed, antibiotics started.
10	795	27 2/7	Increased abdominal girth, visible bowel loops, increased girth. CONS sepsis and meningitis. Occurred while on BM feedings every 3 hrs. Andersen tube placed, antibiotics started.
11	1348	30 2/7	Grossly blood stools, increased abdominal girth, visible bowel loops. KUB showed possible thickened bowel wall, no definite pneumatosis. Occurred while on BM (22 cal/oz) 22 mL every 3 hrs. Andersen tube placed, antibiotics started.
Mean ±SD	1463 ±1012	30.6 ±4.1	

wt = weight; gest = gestational; g=grams; w=weeks; KUB = abdominal radiograph (kidney, ureters, bladder); BM = breast milk.

test solution (or sham) was given, the test solution recipients trended towards receiving slightly more enteral calories than the sham recipients (Table 3). Also, during the seven days after the cessation of the test solution (or sham) administrations, the test solution recipients trended towards receiving more enteral calories than the sham recipients (Table 3). Comparing pre-treatment to post-treatment, test solution recipients had a greater increase in enteral calories received than sham recipients (Table 3). During the seven days after the cessation of the test solution (or sham) administrations, five of the nine-sham recipient had their milk feedings changed to Alimentum (Ross Laboratories, Columbus, OH) or to Alimentum and subsequently to Neocate (Mead Johnson, Evansville, IN), in an attempt to improve feeding tolerance. In contrast, two of the eleven test solution recipients had their milk feedings changed to Alimentum or Neocate; p = 0.10 Fisher Exact). The clinicians making these changes were not aware whether the patient had been receiving test or sham treatments.

Discussion

If a fetus fails to swallow amniotic fluid, the small bowel mucosa develops in a disorganized and rudimentary fashion.[15-17] Experiments of Karnak[16] and Trahair[17] showed that the effect of swallowed amniotic fluid on bowel development comes from the enterocyte growth factors within the fluid, not from the liquid itself. The enterocyte growth factors present in amniotic fluid are also present in colostrum and human milk.[18] However, of these many factors, only rEpo and rG-CSF are currently available in the USA as FDA approved medications. rEpo was first recognized for its anti-apoptotic action on erythrocyte progenitors, but it has been subsequently found to have many other important non-erythropoietic functions during human fetal development. These include that of a neuroprotectant and as an anti-apoptotic factor involved in development of the fetal gastrointestinal mucosa.[19] rG-CSF was first recognized for its capacity to support the clonal maturation of neutrophils from progenitors, but it subsequently was found to have important developmental and trophic actions on the fetal small bowel mucosa.[20]

Table 3. The columns display the 20 subjects according to group (control vs. test solution), age and weight at study entry, days the test solution (or sham) was given, and enteral calories/k/d during three periods; Period #1 = the 3-days before beginning the study; Period #2 = the days during which the treatment (or sham) was given; Period #3 = the 7-days after the treatment (or sham) ended. The last column lists whether a special formula was used during period #3, because of presumed intolerance of breast milk.

Patient no.	*Age when test solution (or sham) was begun (d)*	*Weight when test solution (or sham) was begun (g)*	*Days test solution (or sham) was given (d)*	*Mean enteral cal/k/d during Period #1*	*Mean enteral cal/k/d during Period #2*	*Mean enteral cal/k/d during Period #3*	*Difference in enteral cal/k/d from Period #1 to Period #3*	*Human stopped and "hydrolyzed or elemental" formula used in Period #3*
Control 1	18	1652	5	31.1	16.0	102.1	71.0	Alimentum
Control 2	15	2767	5	0	12.3	65.6	65.6	-
Control 3	21	946	7	0	7.8	3.9	3.9	Alimentum
Control 4	16	2306	4	33.0	11.1	88.6	55.6	Alimentum then Neocate
Control 5	49	1917	7	0	15.3	89.3	89.3	Alimentum then Neocate
Control 6	17	1205	7	17.9	0	15.2	-2.7	-
Control 7	7	3075	5	2.7	22.2	66.9	64.2	-
Control 8	15	1219	7	0	15.0	67.8	67.8	-
Control 9	4	2410	3	0	28.0	88.8	88.8	Alimentun
Mean ± SD (or median*)	18.0±13.0	1944±747	5.6±1.5	*0	14.2±8.0	65.3±4.1	55.9±11.1	5/9
Test 1	13	1134	6	0.3	23.6	106.6	106.3	-
Test 2	20	665	7	0	11.4	44.8	44.8	-
Test 3	11	4259	5	0	40.6	86.2	86.2	Alimentum
Test 4	21	953	7	0	13.7	65.9	65.9	-
Test 5	24	1859	2**	0	2.1	66.9	66.9	-
Test 6	24	1592	5	8.4	12.4	95.7	87.3	-
Test 7	25	1425	6	33.1	56.6	108.6	75.5	-
Test 8	11	2010	4	0	22.2	98.4	98.4	-
Test 9	12	1671	7	11.8	4.2	91.4	79.6	Alimentum then Neocate
Test 10	31	1388	7	0	4.7	45.6	45.6	-
Test 11	14	1537	7	0	19.7	101.4	101.4	-
Mean ± SD (or median*)	18.7±6.9	1681±939	5.7±1.6	*0	19.2±16.6	82.9±23.3 p = 0.11	78.0±6.3 p = 0.05	2/11 p = 0.10

*d = days; g = grams; * = median; ** = test solution inadvertently stopped after 2 days..*

In the present study we enrolled 20 patients who had signs of feeding intolerance, and randomized these to either every three hour oral-gastric (or nasal-gastric) infusions of a test solution patterned after human amniotic fluid and containing rEpo and rG-CSF (test group), or a sham administration (control group). A fetus normally swallows 200 to 300 mL of amniotic fluid per kg body weight each day. We reasoned that if the test solution contained 10 fold higher concentrations of recombinant growth factors than found in normal amniotic fluid, the volume administered could be reduced 10 fold, to 20 mL/kg/day in order to provide the approximate amount of factors to which the fetal intestine is normally exposed.

In the present study, as with the previous phase I studies of this test solution,[4,11-14] the experimental fluid was well tolerated, with up to seven days of every three hour administration. This solution has now been administered to over 100 NICU patients in various clinical trials, and from that experience it appears that the solution is indeed feasible to administer, well tolerated, and without significant short-term safety concerns. However, the issue of efficacy, in diminishing feeding intolerance, remains undetermined, and can only be addressed using an adequately powered randomized, masked or placebo-controlled design. The present study was performed as a needed step toward the goal of designing such a trial. This was the first study of this solution to employ a randomized, masked design, and although only twenty patients were included, the outcomes of interest all showed evidence of improvements among the test solution recipients. Based on the difference of post-treatment enteral calories received between the two study groups, a sample size calculation suggests that 36 neonates per group are needed for an appropriately

powered ($\beta = 0.20$) study.

One limitation of this study is the lack of protocolization of feeding volume increases in neonates after an episode of feeding intolerance. Decisions about the volume of feedings were left entirely to the clinicians on daily rounds, but perhaps a better method would have been to devise a set schedule for escalation of volumes, to try to apply to all of the study subjects.

Another limitation of the study is the heterogeneity of the patients. Essentially every study dealing with feeding problems in the NICU grapples with the pleomorphic nature of the problem. Thus, perhaps it is not unexpected that in the present trial the outcomes varied widely, in both treatment and control groups. Specifically, some of the patients in the control and test groups had little or no subsequent feeding problems, while others continued to have feeding problems for at least a week or more. We predict that because of the heterogeneous nature of feeding intolerance in the NICU, no single new medication is likely to benefit all cases. In fact, we predict that a solution like the one we tested will be helpful only in cases where the intestinal mucosa has undergone significant atrophic changes, amenable to topical growth factor treatment. Precisely which neonates with feeding problems will benefit from a solution such as the one we tested obviously awaits additional investigation.

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