RESEARCH BRIEF

Aggressive Parenteral Nutrition in Sick Very Low Birth Weight Babies: *A Randomized Controlled Trial*

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Survival of preterm neonates in developing world has improved. Developing countries lag behind in nutritional management in NICU especially parenteral nutrition (PN). This randomized controlled trial was done to evaluate the effect of aggressive parenteral nutrition on nitrogen retention of sick VLBW and extremely low birth weight (ELBW) babies. From September 2009 to February 2010, total 34 babies were randomized to receive aggressive parenteral nutrition (APN) (*n*=17) or standard parenteral nutrition (SPN) (*n*=17). The average daily total and PN calory intake of babies in APN group was significantly higher during first week. APN was well-tolerated; however, nitrogen retention was not significantly higher in APN group. Aggressive parenteral nutrition in sick VLBW babies is feasible in developing world, though it did not improve nitrogen retention in first week of life.

Keywords: *Aggressive; Nitrogen retention; Parenteral nutrition; Preterm.*

Owing to advances in perinatal medicine, more very preterm infants are surviving. These babies have unique nutritional requirements for growth due to their low energy stores, high protein accretion rate and high metabolic rate. Compared to advances in other aspects of neonatal care, developing countries lag behind in nutritional management, especially parenteral nutrition [1]. Delay in initiating nutritional support results in postnatal malnutrition that produces measurable growth failure [2,3]. Effects of malnutrition in early life of preterm neonates are long-lasting [4].

Because of immaturity of the gastrointestinal tract, most prematurely born infants must initially be given parenteral nutrition (PN). PN can be given safely shortly after birth (aggressive PN). The purpose of this study was to evaluate the effectiveness and safety of aggressive PN in VLBW infants during the first week of life in comparison with standard PN. We hypothesized that, in comparison to standard PN, aggressive PN would improve nitrogen balance, be well tolerated metabolically, shorten time to regain birth weight and shorten length of hospitalization.

METHODS

This randomized controlled trial was conducted in a 40 bed level III referral neonatal unit. All babies admitted from October 2009 to March 2010 were screened for eligibility. Eligibility criteria were: (*i*) Prematurity (<37 weeks), (*ii*) chronological age <24 hours, (*iii*) birth weight <1500 grams and (*iv*) need for respiratory support (mechanical ventilation or nasal CPAP). Babies with any one of the following were excluded: (*i*) major congenital defects, (*ii*) chromosomal abnormalities, (*iii*) antenatal suspicion of liver and or kidney diseases, (*iv*) enrolment to other trial. If informed consent was obtained from one or both parents within the first 24 hours of life, infants were enrolled. The study protocol was approved by institutional ethics committee.

Babies were randomly allocated to either aggressive PN or standard PN using computer generated random numbers contained in consecutively numbered sealed envelopes with labels wrapped in opaque aluminum foil. The clinical team and statistician were unaware of the assignments. Babies in the standard PN limb received PN as per the unit's existing protocol. It called for intravenous amino acids (Aminoven Infant 10%, Fresenius Kabi, India Ltd) to be started in the first 24 hrs of life in a dose of 1 g/kg. The dose was increased to 2 g/kg the following day and remained the same thereafter. Intravenous lipids (Intralipid 20%, Fresenius Kabi, India Ltd) were introduced on day 3 at a dose of 1 g/kg which remained the same thereafter. The babies assigned to the aggressive PN limb received 3 g/kg of amino acids and 2

g/kg of lipids beginning in the first 24 hrs of life. Unless intolerance developed, infants received the assigned PN until enteral intake reached 80% of total intake. Criteria for intolerance to PN and to terminate PN (if attending physician demands) was predefined. Fluid intake was not dictated by the experimental protocol. Enteral nutrition (20 mL/kg/day) was initiated once babies achieved hemodynamic stability. Human milk was preferred when available, otherwise preterm formula was fed. Feedings were increased by 25 mL/kg/day as tolerated.

Body weight was determined daily on an electronic scale accurate to 2 g (ATCO, Electric Balance, Model LL6MM 06/12-W). Fluid intake and urine volume was recorded daily. Urine was collected from an attached bag with any leakage collected on preweighed diaper.

Nitrogen retention was determined on days 4 and 7 using the standard formula (5). Nitrogen intake was calculated as Amino acids (g) ÷ 6.25 = mg of nitrogen. To monitor tolerance of PN, blood glucose was determined twice daily and serum electrolytes, urea, creatinine, bilirubin, triglycerides, arterial blood gas and full blood count were obtained on days 4 and 7. Determinations were performed in the hospital laboratory using standard methods. The attending neonatologist could order additional tests as needed depending on the clinical condition of baby. Time (in days) to regain birth weight and length of hospitalization were determined from medical records.

Statistical Package for Social Sciences (SPSS version 11.5, Inc. Chicago, USA) for MS windows was used for statistical analysis. Nitrogen retention on day 7 with standard PN, estimated before the start of the trial, was 150 (+/- 80) mg/kg/day. It was hypothesized that aggressive PN would increase this to 300 mg/kg/day on day 7. Sample size of 16 in each group was necessary to detect this difference in the mean nitrogen retention with a power of 80% and a P value < 0.05.

RESULTS

During study period 34 babies met the eligibility criteria and were enrolled with 17 babies in each group. Mean birth weight was 1161.5 (SD 223.8) in the aggressive PN group and 1263.8 (SD 194.4) in the standard PN group. Mean gestational age was 30.5 (2.6) weeks and 32.1 (2.8) weeks, respectively. In both groups 41% babies received antenatal steroids.

Table* I** shows nutritional intakes and outcomes of both groups. Biochemical parameters were comparable in both groups (Table* II**). Clinical outcomes like intraventricular hemorrhage, hemodynamically significant PDA, late onset sepsis, need for exchange transfusion and bronchopulmonary dysplasia were comparable in both groups. Two babies in the aggressive group and one baby in the standard group died before discharge (P=0.9).

DISCUSSION

Though the average daily calorie intake was significantly higher in the aggressive PN group, nitrogen retention in the first week was not significantly increased. Trends were seen toward shorter time to reach full feeds and to regain birth weight and toward shorter duration of stay in NICU. Most importantly, aggressive PN was well tolerated and no adverse clinical and biochemical outcomes were noted.

Early amino acid administration has previously been shown to be safe [6-8]. Early amino acid administration increases protein synthesis, resulting in an anabolic state [9]. Early lipid administration has not been associated with adverse effects in preterm neonates [10,11]. Ibrahim, *et al.* [5] showed that early administration of both amino acids and lipids is well tolerated. Their aggressive approach improved nitrogen balance of preterm babies compared to babies who received late PN. We compared our aggressive approach with the existing

TABLE I NUTRITIONAL OUTCOMES IN THE TWO GROUPS

Outcome	*Aggressive PN group(n=17)*	*Standard PN group(n=17)*	*P value*
Calories received in first week (kcal/kg/d)	63.5 (8.1)	50.1 (11.1)	0.001
PN calories received in first week (kcal/kg/d)	45.8 (9.1)	38.7 (8.6)	0.04
Nitrogen retention on day 4 (mg/kg/d)	411.9 (107.9)	328.7 (197.5)	0.17
Nitrogen retention on day 7 (mg/kg/d)	370.7 (233.6)	278.7 (151.1)	0.69
Time to regain birth weight (d)	9.5 (6.7)	11.5 (6.7)	0.394
Time to reach full enteral nutrition (d)	8.4 (6.9)	11.1 (6.6)	0.23
Duration of NICU stay (d)	19.5 (13.3)	20.2 (12.9)	0.92

All values in ____ (SD); PN: Parenteral Nutrition.

TABLE II BIOCHEMICAL PARAMETERS ON DAY 7 IN THE TWO GROUPS

Parameter	*Aggressive PN group (n=17)*	*Standard PN group (n=17)*
pH	7.4 (0.08)	7.4 (0.10)
Bicarbonate (mmol/L)	16.7 (2.4)	18.7 (2.5)
S. urea (mg/dL)	36.2 (25.4)	24.7 (12.9)
Urine urea (mg/dL)	483.0 (400.0)	346.0 (411.2)
S. triglycerides (mg/dL)	153.9 (70.2)	94.8 (60.2)
S. bilirubin (mg/dL)	6.7 (3.1)	7.2 (2.5)

*S: Serum; Mean (SD), P; *: P=0.05.*

PN regimen, where infants received amino acids from day one but at a lower dose than with the aggressive regimen. Nitrogen excretion increases in babies when nitrogen intake increases [8]. We noted a similar finding. There was also nitrogen coming from enteral feedings which probably increased urinary nitrogen excretion and explains why apparent nitrogen retention was less. This may be one of the reasons why we could not show significant improvement in nitrogen retention.

Recent studies have demonstrated better growth in VLBW babies receiving aggressive nutrition [7,12-14]. We could not find an effect of aggressive PN on time to regain birth weight. Most babies in the aggressive PN group were on full enteral feeds by the ninth day. But as per unit policy, most babies did not receive fortified milk till the end of second week. There are other factors influencing weight in the first week of life. These may be the reason why we did not find an effect on time to regain birth weight. Valentine, *et al.* [7] observed that babies receiving early amino acids achieved full enteral feedings earlier despite being smaller and younger at birth. We noticed a similar trend, though it was not significant. In developing countries like India, social and economic reasons affect the time of discharge. So we could not show any effect on duration of NICU stay.

One important observation was that babies tolerated aggressive PN well. Neonatologists in developing countries like India, are still concerned about the safety of PN, as there is lack of data from the developing world. We can say that aggressive and early PN is feasible and safe in India. This may be taken as a positive step. Larger multicentric trials are needed before reaching conclusions about efficacy. Our study suggests that aggressive PN is safe in India.

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