

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Can an Alternative Umbilical Arterial Catheter Solution and Flush Regimen Decrease Iatrogenic Hemolysis While Enhancing Nutrition? A Double-Blind, Randomized, Clinical Trial Comparing an Isotonic Amino Acid With a Hypotonic Salt Infusion

Jodi K. Jackson, Deborah J. Biondo, Janice M. Jones, Pamala J. Moor, Stephen D. Simon, Robert T. Hall and Howard W. Kilbride

Pediatrics 2004;114:377-383

DOI: 10.1542/peds.114.2.377

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/114/2/377>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2004 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Can an Alternative Umbilical Arterial Catheter Solution and Flush Regimen Decrease Iatrogenic Hemolysis While Enhancing Nutrition? A Double-Blind, Randomized, Clinical Trial Comparing an Isotonic Amino Acid With a Hypotonic Salt Infusion

Jodi K. Jackson, MD; Deborah J. Biondo, MS, RD, LD, CNSD; Janice M. Jones, RN, NNP; Pamala J. Moor, RN, NNP; Stephen D. Simon, PhD; Robert T. Hall, MD; and Howard W. Kilbride, MD

ABSTRACT. *Objective.* In the process of sampling blood through an umbilical arterial catheter (UAC), infant blood comes into stagnant contact with infusion solution in the “waste syringe” before being reinfused. We have previously demonstrated *in vitro* that this process is associated with less hemolysis of red blood cells (RBCs) with use of an isotonic solution compared with a hypotonic 0.25 normal saline (NS) solution. The objective of this study was to compare the *in vivo* effect on hemolysis of 2 UAC infusion/flush regimens (an isotonic regimen vs a hypotonic regimen) and to assess the early nutritional benefit of an amino acid solution as the isotonic UAC infusion solution.

Methods. Infants who had a birth weight of ≤ 1.5 kg and were expected to have a UAC for ≥ 3 days were enrolled within 24 hours of life into this prospective, double-blind, randomized, clinical trial of 2 UAC infusion solution/flush regimens. Power analysis demonstrated that 40 infants were needed to determine differences in hemolysis quantified by plasma-free hemoglobin (PFH) level. Nutrition from glucose was evaluated by measurement of daily dextrose calories. C-peptide was measured to evaluate endogenous insulin production. Adverse events and protein tolerance were tracked.

Results. Twenty-two infants (mean gestational age: 27 weeks; 945 g birth weight) were enrolled in each group, for an average of 4.2 days (range: 2.5–8 days). There were no group differences in demographics. PFH levels were lower for infants who received isotonic amino acid (IAA) in comparison with 0.25 NS (33 ± 14 mg/dL vs 62 ± 27 mg/dL, respectively). C-peptide was higher in those who received IAA, as were nonprotein calories received on days 4 to 6 of the study (51 ± 11 kcal/kg/day vs 44 ± 12 kcal/kg/day, IAA vs 0.25 NS, respectively).

Conclusions. Lower PFH levels in IAA versus 0.25 NS group were consistent with our hypothesis of decreased hemolysis with an isotonic infusion/flush regimen. IAA use may also allow greater early glucose nutrition, as indicated by the higher level of endogenous insulin production and improved glucose tolerance. IAA seems to be a superior UAC solution to 0.25 NS in that it is associated with less hemolysis and improved nutrition. *Pediatrics*

2004;114:377–383; umbilical arterial catheter, amino acid solution, hemolysis, infusion solution, neonate.

ABBREVIATIONS. UAC, umbilical arterial catheter; RBC, red blood cell; NS, normal saline; IAA, isotonic amino acid; TPN, total parenteral nutrition; PFH, plasma-free hemoglobin; BUN, blood urea nitrogen; BE, base excess; CBC, complete blood cell count; CI, confidence interval

In the critically ill infant, an umbilical arterial catheter (UAC) is often used for access to blood for sampling (Fig 1). There must be a constant infusion through this line to avoid clotting. A “waste syringe” is used to clear the line of infusion solution before a sample is taken. During this process, the syringe will have a mixture of blood and infusion solution in stagnant contact for ~ 60 seconds. After the sample is taken, the waste is reinfused, followed by a flush. The flush comes into isolated contact with the waste in the tubing. The damaging effect that the infusion solution may have on red blood cells (RBCs) occurs during this contact in the waste syringe, when clearing the line, and in the tubing, when flushing takes place.¹

Because there is little clinical evidence on the subject, there is no uniform approach within the community of practice as to which infusion solution is best.^{2,3} However, a recent informal survey of 20 centers involved in the Vermont Oxford Collaborative revealed that 33% used 0.25 normal saline (NS), 33% used 5% dextrose (D₅W), 27% used 0.5 NS, and 6% used NS. Many centers avoid an isotonic saline solution because of the concern that a large sodium intake in the first days of life may be associated with increased extracellular fluid volume and bronchopulmonary dysplasia.^{4,5} Dextrose-containing solutions may contribute to hyperglycemia and also affect blood sugar determinations of the arterial line samples. In addition, when dextrose-containing solutions come into stagnant contact with RBCs, as occurs in the waste syringe during blood sampling, macroscopic agglutination occurs.^{6,7} This agglutination is reversible with the addition of salt or base, but there is irreversible damage to the cells involved in the agglutination, which leads to their premature destruction.^{7–9} Hemolysis without agglutination also occurs when blood comes into stagnant contact with

From the Department of Pediatrics, Section of Neonatal-Perinatal Medicine, Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri.

Received for publication Jan 6, 2003; accepted Dec 10, 2003.

Reprint requests to (J.K.J.) Children's Mercy Hospital and Clinics, 2401 Gillham Rd, Kansas City, MO 64108. E-mail: jjackson@cmh.edu
PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

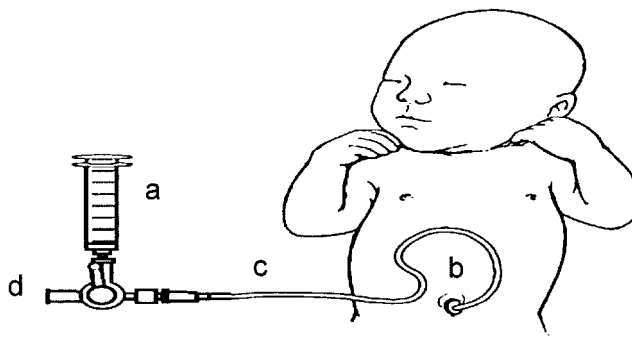


Fig. 1. Umbilical arterial catheter setup for the sampling of blood: waste syringe (a); UAC insertion site (b); UAC tubing (c); continuous infusion line connection site (d). The waste syringe (a) is used to clear the line of infusion solution before a sample is taken. After the sample is taken, the waste is reinfused, followed by a flush. The infusion solution comes into stagnant contact with blood in the waste syringe (a), and the flush comes into isolated contact with the waste (containing a mixture of blood and infusion solution) in the tubing (c).

solutions of dextrose and varied salt concentrations as a result of a direct effect of the dextrose on the RBCs.^{9–11}

Although diluted saline (eg, 0.25 NS, as used by 33% of centers surveyed) may not affect dextrose measurement or supply an abundance of sodium, when mixed with adult RBCs, hemolysis occurs, which is accentuated by prolonged contact time and with increasing ratio of solution to blood.^{12–14} It seems by the use of 0.25 NS and 0.5 NS as UAC infusions in many centers that it is believed that none or only negligible hemolysis might occur when using a hypotonic solution for UAC infusion. However, our *in vitro* model confirmed that even very brief contact of placental RBCs with hypotonic solutions (60 seconds in the waste syringe) leads to significant hemolysis.¹ Pilot data (not published) has shown that the blood exposed to the hypotonic solution in the tubing during flushing is hemolyzed to an even greater extent than that exposed in the waste syringe during sampling, although a smaller volume is exposed.

Excess sodium load, agglutination from sugar solutions, and hemolysis from hypotonic solutions may be avoided by infusing an isotonic amino acid (IAA) solution through the UAC. Early amino acid administration seems to be biochemically safe and has the effect of modifying energy metabolism by stimulating insulin production.^{15,16} The infant who receives amino acids tolerates more exogenous glucose, which may enhance energy intake in the first days of life.¹⁵ The early delivery of amino acids has also been shown to improve nitrogen balance.^{15–21} Supplemental protein may ameliorate adaptive metabolic processes that occur in the sick, premature infant and protect against the loss of as much as 3% per day of total body protein.¹⁶ There is evidence that concentrations up to 2.5 mg/kg/day of amino acids are safe to infuse from the first day of life.^{15–22} Our *in vitro* data have shown much less hemolysis (0.8%) when this isotonic solution comes in contact with neonatal blood, when compared with 0.25 NS (5.4% hemolysis).¹

We hypothesized that the infusion of an IAA solution into the UAC would be associated with less hemolysis of infant RBCs while providing a nutritional benefit. The objective of this study was to compare the effect of 2 UAC infusion/flush regimens on hemolysis *in vivo* and to assess the early nutritional benefit of an amino acid solution as the isotonic UAC infusion.

METHODS

Participants

This double-blind, randomized study involved infants in 2 intensive care nurseries in Kansas City, Missouri. Center 1 was a level 2+ inner-city, county hospital with ~2500 births per year, and center 2 was a regional referral children's hospital. Eligible infants were all those who had birth weight ≤ 1500 g, were < 24 hours of age, had a UAC in place and were expected to need the UAC for at least 3 days. Infants were stratified into 2 birth weight categories: < 1 kg and ≥ 1 kg. Exclusion criteria were the infusion of a UAC solution > 24 hours before entering the study, known hemolytic disease, or extensive bruising. All infants received the unit's standard UAC solution (0.25 NS) before enrollment.

Interventions

Infants were randomized to receive either standard (0.25 NS) UAC flush and infusion solutions (control) or an IAA UAC infusion solution and a 0.5 NS flush solution (study). The 0.5 NS flush has been shown to produce no more hemolysis than IAA¹ and provided only an additional 0.04 mEq sodium per each 0.5 mL flush, avoiding both the high sodium load of NS and the periodic bolus of amino acids. UACs all were placed in the "high position" (between the thoracic vertebrae 6 and 9). The above-stated infusion and flush were the only fluids infused in these lines. No medications or hyperalimentation was ever given through these UACs.

The IAA solution was produced by using 10% TrophAmine (Braun Medical, Irvine, CA), diluted to be isotonic with blood. Our parameters for choosing a solution were that it have no more sodium than 0.25 NS and not deliver an excess of nitrogen in relation to nonprotein calories. For infants 0.5 kg to 0.999 kg, we used 2.65% TrophAmine solution, generated by diluting 10% TrophAmine with a sodium solution to a final osmolarity of 305 mOsm/L and sodium concentration of 38.5 mEq/L. The UAC solution ran at a rate of 1 mL/hour to give 24 mL/day, which provided 0.64 g of protein. This supplied a range of protein of 0.64 to 1.27 g/kg/day for the infants in this weight range.

For infants 1 kg to 1.5 kg, a 3.5% TrophAmine solution was used, produced by diluting 10% TrophAmine with water to generate a solution that was 306 mOsm/L, with 1.8 mEq/L of sodium. This solution was infused at 1.5 mL/hour for a total of 36 mL/day, which provided 1.26 g of protein and supplied a range of protein of 0.84 to 1.26 g/kg/day for the infants in this category. Infants remained in their originally assigned weight category regardless of weight change during the study. Total parenteral nutrition (TPN), infused through the venous line, was started at the discretion of the individual caregivers, following usual clinical practice for advancing calories and composition.

Outcome/Sample Size

The primary outcome was hemolysis measured by plasma-free hemoglobin (PFH). On the basis of preliminary data, it was estimated that 40 subjects were needed to give this study a power of 80% to show a change in PFH of 40%. This study was also projected to have the power to evaluate the secondary outcomes of glucose and protein tolerance. On the basis of previous reports, it was projected that 40 subjects would give 86% power to show a change of 40% in glucose tolerance and a difference of 1 SD in measures of protein tolerance (creatinine, blood urea nitrogen [BUN], and metabolic acidosis measured by base excess [BE]).

Criteria for removing an infant from the study were elevated BUN (> 38 mg/dL), creatinine (> 2 mg/dL), or acidosis (BE < -10 mmol/L). If 5 infants were removed, then the study would be stopped pending an impartial review.

Daily measurement of basal metabolic parameters (sodium,

potassium, chloride, bicarbonate, creatinine, and BUN), arterial blood gases, and complete blood cell count (CBC) were performed per routine care. In addition, PFH levels were obtained daily for the duration of the study. On day 3 of the study, a C-peptide level was obtained as a measure of endogenously produced insulin, which is thought to be increased with the early administration of protein.¹⁵ Subjects remained in the study until the UAC was removed or until protein provided by the TPN exceeded 2 g/kg/day. Therefore, assuming that all infants were receiving the maximum protein that could be given in the UAC solution, the total protein provided never exceeded 3.4 g/kg/day. Nutritional and electrolyte data were collected for 7 days. Short-term outcome data were collected throughout the study to evaluate for trends.

Randomization/Allocation/Implementation

After parental consent was obtained, infants were randomized and treatment group was allocated by the pharmacy, using a random number generation method (stratified on the basis of birth weight category), grouped in blocks of 4. The solutions were prepared by a pharmacist and were blinded to all who were involved in clinical care. Only after the predesignated number of infants had enrolled in the study and their data were evaluated was the identity of the solution revealed.

Blinding/Masking

Bags of infusion solution and flush were delivered to the bedside with labels identifying them as "test solutions" only. Both the study and the control group solutions appeared identical in these bags.

Statistical Methods

Daily values for all outcome measures were averaged across all days in the study period. The primary analysis combined data in both weight groups and were compared by treatment group. A secondary analysis examined each weight group separately. In

addition, trends for individual days were examined graphically. The data were analyzed using a 2-sided *t* test, analysis of variance, and 2-sided Fisher exact test using SPSS version 10 (SPSS Inc, Chicago, IL). The exact difference and confidence interval (CI) for proportions were evaluated using STATXact software (Cytel Software Corp, Cambridge, MA). C-peptide was evaluated using the log value because of the skewed nature of the measurement. Data for continuous outcomes are presented as mean \pm SD.

RESULTS

Participant Flow/Number Analyzed

Figure 2 shows details of eligibility and enrollment flow. There were 2 protocol deviations. In one, an infant was enrolled at a weight 141 g above the entry criteria, because of his twin brother's enrollment. The second was started on full TPN at 12 hours of life, which is not the usual practice in the intensive care nursery and, as such, was a violation of the protocol specifying basic TPN initiation at 2 to 3 days of life. This patient was removed from the study at 18 hours of life, but data were analyzed by intention to treat.

Only 1 infant was excluded from analysis, as a result of an error in allocation by the pharmacy. The infant was randomized and allocated to the control group initially but then to the study group on the subsequent day.

Because of the participation of a children's hospital in the study, with an outborn population, the time between placement of the UAC and enrollment in the study was 1 to 24 hours. All patients received the

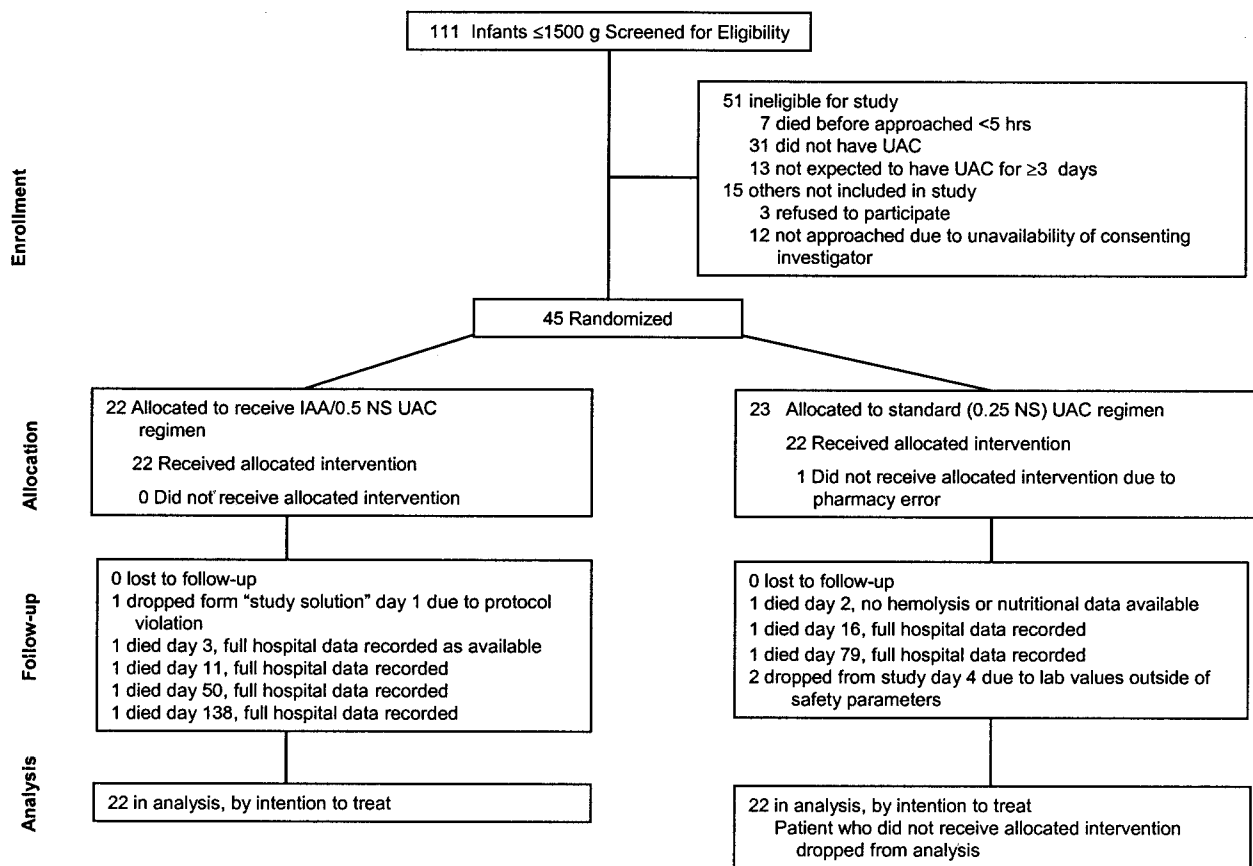


Fig. 2. Enrollment flow diagram. This flowchart diagrams the patient flow through screening for eligibility through enrollment, allocation, follow-up, and analysis.

TABLE 1. Demographics of Study Population

	Control	Study
N		
Total	22	22
<1 kg	13	13
>1 kg	9	9
GA, wk		
Total	27 ± 2.0	27 ± 2.0
<1 kg	26 ± 1.4	26 ± 1.4
>1 kg	29 ± 1.3	29 ± 1.8
Birth weight, g		
Total	927 ± 298	948 ± 290
<1 kg	725 ± 179	747 ± 113
>1 kg	1218 ± 151	1237 ± 203
Days on study solution		
Total	4.0 ± 1.7	4.3 ± 1.8
<1 kg	4.8 ± 1.9	4.7 ± 2.0
>1 kg	3.1 ± 0.8	3.7 ± 1.4
1-Min Apgar <1		
Total	0 (0%)	3 (14%)
<1 kg	0 (0%)	2 (15%)
>1 kg	0 (0%)	1 (11%)

GA indicates gestational age. Continuous data presented as mean ± SD; categorical data presented as n (%).

unit's standard infusion/flush solutions (0.25 NS) before study enrollment.

Recruitment

All eligible participants were recruited from September 1, 2000, to October 8, 2001, when the predesignated study number for enrollment was met. Data collection continued throughout the hospital course of enrolled infants, with final date of study January 15, 2002.

Baseline Data

Baseline demographics and clinical characteristics of each group are shown in Table 1. The 2 groups were similar on all measurements. However, Apgar scores showed a trend toward more compromise in the study subjects, with more subjects in the study group having a 1-minute Apgar score <1. Mean 1-minute Apgar score was 5 ± 2.8 versus 4 ± 2.9, control and study, respectively (P = .37). Mean 5-minute Apgar score was 7 ± 1.7 versus 5 ± 2.7, control and study, respectively (P = .01).

Outcomes

The mean PFH level during the study period was significantly higher in the control group compared with the study group (Table 2, Fig 3). The control group had a higher mean PFH on each day of the

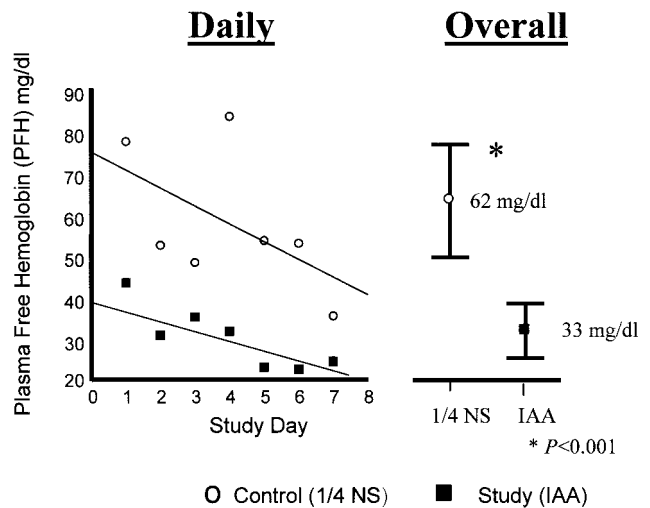


Fig. 3. PFH by study day and overall. This is a graphic representation of the changes in PFH over days in the study. ○, mean PFH level of the control group on each day of the study; ■, the same for the study group. The CIs represent the average PFH over the whole study period.

study (Fig 3). The average number of blood draws per day was not different by group (6.08 ± 2.1 vs 6.26 ± 1.9 control and study, respectively; 95% CI: -1.1 to 1.5; P = .77). There was a linear relationship between number of blood draws and PFH in both groups, with an increase in PFH with increased blood draws (r² = 49% and r² = 56%, control and study groups, respectively). However, the slope of the increase in PFH was greater in the control group than in the study group (with an increase in PFH of 7.2 mg/dL/blood draw vs 2.6 mg/dL/blood draw, control and study, respectively; 95% CI: -9 to -0.08; P = .046; Fig 4).

When data were analyzed by birth weight, PFH levels remained higher for control infants in both subgroups: <1 kg, 67 ± 30 mg/dL vs 35 ± 14 mg/dL (95% CI: -52 to -13; P = .002), and >1 kg, 54 ± 23 mg/dL vs 30 ± 13 mg/dL (95% CI: -43 to -6; P = .014), control and study groups, respectively.

Glucose tolerance, shown as kcal/kg/day of glucose, was higher on days 4 to 6 in the IAA group (Table 2). The C-peptide level in the IAA group was significantly higher, consistent with the elevated glucose tolerance (Table 2). By set study design, protein nutrition was also greater in the study group. During the 7-day period, the control group received 40% less protein than the study group.

TABLE 2. Control Versus Study Group for Primary and Secondary Outcome Measurements

	Control 0.25 NS	n*	Study IAA	n	Mean Difference	95% CI	P Value
PFH, mg/dL	62 ± 27	21	33 ± 14	22	-29	-42 to -16	<.001
Glucose nutrition (kcal/kg/day) days 4-6†	44 ± 9	21	51 ± 9	20	7	1.5 to 13	.014
Log C-peptide, ng/mL‡	0.17 ± 0.30	21	0.35 ± 0.27	21	0.18	0.0004 to 0.35	.05
Protein (g/kg/day) days 1-7	0.77 ± 0.40	21	1.23 ± 0.31	22	0.47	0.25 to 0.69	<.001

Data are mean ± SD.

* Control group n = 21 as 1 patient died early in study and data were not collected for these data points.

† Study group n = 20 as 1 patient died before data were collected and another patient was dropped from study as a result of pharmacy error and data were not collected for this parameter.

‡ Study group n = 21 as a result of patient exit of study.

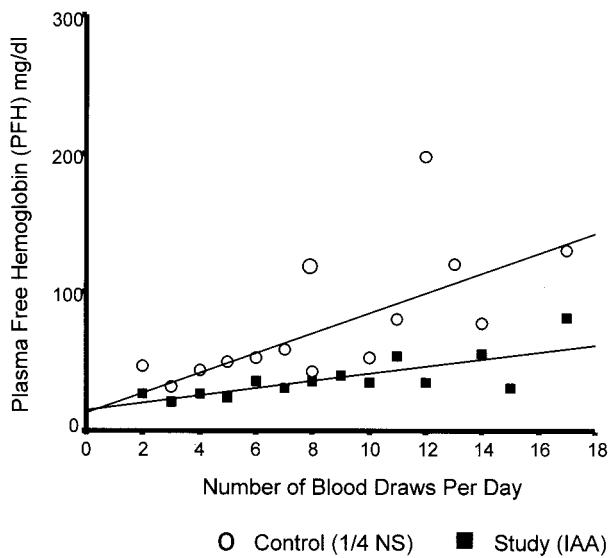


Fig. 4. PFH versus number of blood draws. Correlation between the number of blood draws per day and PFH. ○, mean PFH level of the control group for each number of blood draws; ■, the same for the study group.

There were no significant differences in measures of protein tolerance, specifically, BE, BUN, and creatinine values averaged over the study period (Table 3). Within the <1 kg birth weight group, there was a difference in urine output, fluid intake, and mean serum sodium concentration during the first week (Table 3). The differences in these parameters occurred mostly on the first days of the study and seemed to be associated temporally. Three infants in the control group had critically low sodium levels (<130 mmol/L), and none had critically high levels. In the study group, there was 1 critically low sodium level and 3 critically high values (>150 mmol/L). A

comparison of serum potassium levels in the <1 kg subgroup demonstrated higher levels in the control group during the first 2 days of the study (Fig 5).

Short-term outcome measures were assessed for surviving infants (Table 4). No significant differences were seen in length of hospitalization, discharge weight, or serious morbidities (Table 4). No infants in either arm of the study had the UAC removed as a result of catheter-related complication or aortic thrombus. During the 1-year period in which study enrollment took place, 5 infants had their UAC removed as a result of documented aortic thrombus. None of these infants was involved in the study, and at least 3 may have had predisposing surgical issues.

DISCUSSION

This randomized trial of an isotonic UAC infusion with 0.5 NS flush showed a decrease in PFH compared with a hypotonic infusion/flush regimen, consistent with our previous in vitro work.¹ Although the degree of hemolysis estimated to have occurred was not enough to significantly affect need for transfusion, the PFH levels within the first days of life for these preterm infants were higher than anticipated (normal: 5-30 mg/dL in healthy term newborns).²³ PFH levels have not previously been evaluated in the population of sick premature infants, but elevated PFH has a number of theoretic risks for this population.^{24,25}

The brief mixing of a hypotonic fluid with RBCs, which occurs with blood sampling through a UAC, is associated with significantly increased hemolysis.¹ Additional pilot data (unpublished) have shown that the blood that is exposed to a hypotonic solution during flushing is hemolyzed to a greater extent (although a smaller volume of blood is exposed) than what occurs in the waste syringe. These data support

TABLE 3. Control Versus Study Group for Metabolic and Fluid Balance Parameters

	Control 0.25 NS	n	Study IAA	n	Mean Difference	95% CI	P Value
Na, mmol/L							
<1 kg	136 ± 2.2	13	141 ± 3.4	13	4.8	2.5 to 7	<.001
>1 kg	139 ± 1.6	9	137 ± 4.2	9	-1.9	-5 to 1.2	.218
Intake, mL/kg/day							
<1 kg*	94 ± 19.7	12	117 ± 24.3	13	23.4	5.0 to 41.7	.015
>1 kg	91 ± 23.9	9	93 ± 27.0	9	2	-23 to 28	.862
Output, mL/kg/hour							
<1 kg*	3.5 ± 0.77	12	4.4 ± 0.93	13	0.92	0.21 to 1.6	.013
>1 kg†	4.0 ± 1.00	9	3.8 ± 0.58	8	-0.2	-1.1 to 0.6	.565
Daily weight change (g/day; in first week)							
<1 kg*	-7 ± 14.3	12	0.06 ± 11	12	7	-3.8 to 17.9	.19
>1 kg†	-13.4 ± 28.4	9	-19.2 ± 17.2	8	-5.8	-30.5 to 18.9	.624
BE, mmol/L							
<1 kg	-3.5 ± 2.25	13	-3.8 ± 1.97	13	-0.26	-2.0 to 1.4	.758
>1 kg	-2.58 ± 1.48	9	-3.51 ± 1.69	9	-0.93	-2.5 to 0.66	.231
BUN, mg/dL							
<1 kg	20 ± 7.7	13	24 ± 10.0	13	3.7	-3.6 to 10.9	.306
>1 kg	23 ± 11.4	9	23 ± 5.5	9	0.24	-8.7 to 9.2	.955
Creatinine, mg/dL							
<1 kg	1.1 ± 0.26	13	1.0 ± 0.18	13	-0.09	-0.27 to 0.1	.337
>1 kg	1.1 ± 0.39	9	1.0 ± 0.14	9	-0.08	-0.37 to 0.21	.571

Data are mean ± SD; all values measured and averaged over a 7-day period.

* Control group, n = 12 because 1 patient died early in study and data were not collected for these parameters.

† Study group, n = 8 because 1 patient was dropped from study and data were not collected for this parameter.

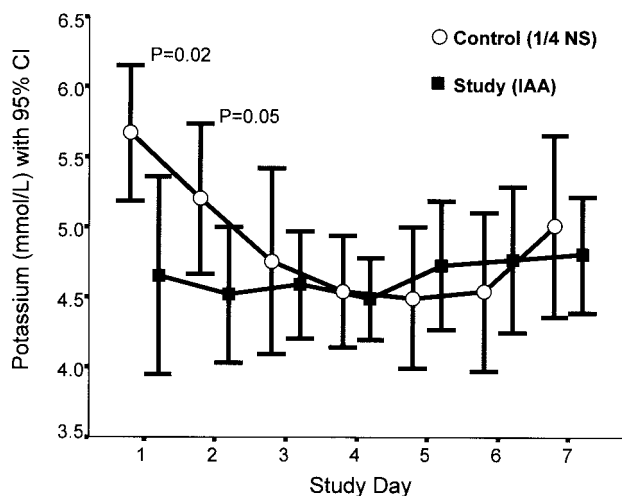


Fig. 5. Serum potassium versus day of study. A comparison in potassium level in the <1 kg subgroup demonstrates lower potassium in the IAA group during the first 2 days of the study, which may reflect the lower level of hemolysis in that group.

the use of a more isotonic solution for infusion and flushing. We chose IAA as the infusion solution because it provided an isotonic infusion while avoiding the infusion of excess sodium of a saline solution and the agglutination problem of a sugar solution. We chose 0.5 NS rather than IAA as the flush solution to avoid the periodic bolusing of amino acids with flushing, which would make it difficult to regulate and quantify the amount of AA received in a 24-hour period. Sicker, smaller infants who had many blood draws would receive more AA (through flushing in addition to the continuous infusion) than an infant who had fewer blood draws. This would make it difficult to interpret measures of protein tolerance, as well as the ratio of protein-to-nonprotein calories. The 0.5 NS flush provided only 0.04 mEq of sodium with each flush, and by estimates of our previous study,¹ one seventh the degree of hemolysis associated with 0.25 NS.

Infants in the study group tolerated a higher glucose infusion rate, had higher C-peptide levels, and tolerated early protein administration. Recent literature supports early delivery of amino acids with up to 2.5 g/kg/day of amino acids seeming to be biochemically safe.^{15–22,26} Infants who receive early amino acids have improved protein balance and tol-

erate more exogenous glucose and, therefore, are able to receive more caloric intake in the first days of life.¹⁵ An additional advantage of infusing IAA through an arterial rather than a venous line is that the delivery of protein is not affected by variations in rate that occur with the delivery of medications and other fluids through the venous line.

Elevated serum potassium levels in the first days of life are commonly seen in extremely low birth weight infants.²⁷ Infants who weighed <1000 g in the control group had increased potassium levels in association with increased PFH compared with the study group. The added hemolysis demonstrated with the hypotonic UAC regimen may contribute to potassium load by increased release of intracellular potassium. Alternatively, the higher production of insulin (evident by increased level of C-peptide measured) in the study group may contribute to the movement of potassium intracellularly and therefore a lower serum concentration. In addition, increased PFH may lead to renal deposition with secondary renal dysfunction and decreased potassium clearance.^{28,29} This hypothesis is supported by relative oliguria and hyponatremia in the <1 kg infants in the control group compared with the isotonic infusion group, despite higher Apgar scores in the control group. It is unlikely that the difference in serum sodium levels between the groups was related to the small amount (0.04 mEq) of extra sodium received with each flush by infants in the study group.

On the basis of data from our *in vitro* study,¹ this study was powered to show a 40% difference in PFH between the 2 groups. This proposed difference in PFH was based on estimates of PFH generation through hemolysis and expected PFH systemic clearance. However, the difference seen in PFH between the 2 groups was much larger than expected. The persistence of elevated PFH observed suggests that additional study of the clearance process of PFH may be indicated in the population studied. Moreover, the dramatically elevated level of PFH generated is likely to be detrimental.^{24,25}

In summary, a regimen involving IAA infusion and 0.5 NS flush for UAC management was associated with less hemolysis, as measured by lower PFH levels, than a regimen of 0.25 NS infusion and flush. Furthermore, the IAA infusion allowed for greater early glucose nutrition, as indicated by the higher

TABLE 4. Control Versus Study Group for Short-Term Outcomes

	Control 0.25 NS	Study IAA	Difference	95% CI	P Value
N	19	18			
DC DOL, d	72 ± 30	75 ± 28	3	–16 to 23	.7
DC weight, kg	2.3 ± 0.5	2.5 ± 0.5	0.12	–0.2 to 0.4	.4
DOL regained birth weight, d	14 ± 6	11 ± 4.5	–3	–6.8 to 0.6	.1
Grade 3–4 ICH	3/19 (16%)	5/18 (28%)	14%	–21 to 46	.71
NEC	2/19 (11%)	3/18 (17%)	6%	–26 to 39	.66
Positive blood culture	2/19 (11%)	3/18 (17%)	6%	–26 to 39	.66
PDA	6/19 (32%)	7/18 (39%)	7%	–26 to 43	.74
Died	3/22 (14%)	4/22 (18%)	4%	–25 to 34	.71

DC indicates discharge; DOL, day of life; ICH, intracranial hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

Excludes infants who died. Continuous data given as mean ± SD; categorical data given as n/N (%).

level of endogenous insulin production and improved glucose tolerance, as well as improved protein nutrition for low birth weight infants in the first days of life. We recommend the use of an IAA infusion solution and that extremely hypotonic infusion solutions and flushes be avoided.

ACKNOWLEDGMENTS

We thank Carey Ehlert, MD, Mark Sheffield, MD, Susannah Ford, MD, and Sherri Leeks, NNP, for assistance in enrollment; Mick Brod, MT, Uttam Garg, PhD, Randah Althahabi, MT, Debbie Lambert, MLT, Nancy Reddig, MT, Karen Meek, MT, and Virginia Darlewon, MT, for laboratory assistance; Pamela Hale, RPh, Cheryl Alley, RPh, and Jonathan Frieze, RPh, for pharmacy assistance and randomization; the bedside nurses at Children's Mercy Hospital and Truman Medical Center for assistance in sample collection; Douglas Derleth, MD, for initial inspiration; and Sue Teasley, RN, Michelle Rooney, RN, and Betsi Anderson, RN, for data management assistance. Thank you to Stuart Jackson, PhD, MBA, and Jacob Jackson for general support and assistance with figure generation.

We dedicate this article to the memory of Mick Brod, MT, Supervisor, Chemistry Laboratory, who passed away on September 29, 2003. His facilitation, commitment, and energy allowed this study to take form and to be completed.

REFERENCES

- Jackson JK, Derleth DP. Effects of various arterial infusion solutions on red cells in the newborn. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F130-F134
- Fletcher MA, Brown DR, Landers S, Seguin J. Umbilical arterial catheter use: report of an audit conducted by the Study Group for Complications of Perinatal Care. *Am J Perinatol.* 1994;11:94-99
- Hodding JH. Medication administration via the umbilical arterial catheter: a survey of standard practices and review of the literature. *Am J Perinatol.* 1990;7:329-332
- Costarino AT, Gruskay JA, Corcoran L, Polin RA, Baumgart S. Sodium restriction versus daily maintenance replacement in very low birth-weight premature neonates: a randomized, blind therapeutic trial. *J Pediatr.* 1992;120:99-106
- Lorenz JM, Kleinman LI, Ahmed G, Markarian K. Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. *Pediatrics.* 1995;96:484-489
- Strautz RL, Nelson JM, Meyer EA, Shulman IA. Compatibility of AD-SOL-stored red cells with intravenous solutions. *Am J Emerg Med.* 1989;7:162-164
- Jones JH, Kilpatrick GS, Fanks EH. Red cell aggregation in dextrose solution. *J Clin Pathol.* 1962;15:161-162
- Weisz-Carrington P. Incompatible intravenous fluids: their potential effect on blood and blood transfusion. In: Gambino SR, Batsakis JG, eds. *Check Sample (Immunohematology 31)*. Chicago, IL: American Society of Clinical Pathologists Continuing Education Program; 1988:1-5
- Ryden SE, Oberman HA. Compatibility of common intravenous solutions with CPD blood. *Transfusion.* 1975;15:250-255
- DeCesare WR, Bove JR, Ebaugh FG. The mechanism of the effect of iso- and hyperosmolar dextrose-saline solutions on in vivo survival of human erythrocytes. *Transfusion.* 1964;4:237-250
- Easton DJ, Ternoey CM. Hemolysis of donor red cells in "two thirds-one third" solution. *Transfusion.* 1985;25:85
- Krzyzaniak JF, Alvarez Nunez FA, Raymond DM, Yalkowsky SH. Lysis of human red blood cells. 4. Comparison of in vitro and in vivo hemolysis data. *J Pharm Sci.* 1997;86:1215-1217
- Krzyzaniak JF, Raymond DM, Yalkowsky SH. Lysis of human red blood cells 1: effect of contact time on water induced hemolysis. *PDA J Pharm Sci Technol.* 1996;50:223-226
- Whitelaw JP. Hemolysis caused by half-physiologic-strength saline. *Transfusion.* 1990;30:78
- Rivera A, Bell EF, Bier DM. Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life. *Pediatr Res.* 1993;33:106-111
- Rivera A, Bell EF, Stegink LD, Ziegler EE. Plasma amino acid profiles during the first three days of life in infants with respiratory distress syndrome: effect of parenteral amino acid supplementation. *J Pediatr.* 1989;115:465-468
- Murdock N, Crighton A, Nelson LM, Forsyth JS. Low birthweight infants and total parenteral nutrition immediately after birth.II. Randomized study of biochemical tolerance of intravenous glucose, amino acids, and lipid. *Arch Dis Child Fetal Neonatal Ed.* 1995;73:F8-F12
- Anderson TL, Muttart CR, Bieber MA, Nicholson JF, Heird WC. A controlled trial of glucose versus glucose and amino acids in premature infants. *J Pediatr.* 1979;94:947-951
- Hammer C, Aramburo MJ. Decreased lipid intake reduces morbidity in sick premature neonates. *J Pediatr.* 1988;113:1083-1088
- Saini J, MacMahon P, Morgan JB, Kovar IZ. Early parenteral feeding of amino acids. *Arch Dis Child.* 1989;64:1362-1366
- Rubecz I, Mestyan J, Varga P, Klujber L. Energy metabolism, substrate utilization, and nitrogen balance in parenterally fed postoperative neonates and infants. The effect of glucose, glucose + amino acids, lipid + amino acids infused in isocaloric amounts. *J Pediatr.* 1981;98:42-46
- Thureen PJ, Anderson AH, Baron KA, Melara DL, Hay WW Jr, Fennessey PV. Protein balance in the first week of life in ventilated neonates receiving parenteral nutrition. *Am J Clin Nutr.* 1998;68:1128-1135
- Koepke JA. Free hemoglobin determinations. *MLO.* 1987;January:13
- Sullivan JL. Iron, plasma antioxidants, and the 'oxygen radical disease of prematurity.' *Am J Dis Child.* 1988;142:1341-1344
- Fink MP. On hemoglobin, hemorrhage, hypotension, and ... nitric oxide. *Crit Care Med.* 1998;26:991-992
- Berry MA, Abrahamowicz M, Usher RH. Factors associated with growth of extremely premature infants during initial hospitalization. *Pediatrics.* 1997;100:640-646
- Shaffer SG, Kilbride HW, Hayden LK, Meade VM, Warady BA. Hyperkalemia in very low birth weight infants. *J Pediatr.* 1992;121:275-279
- Ohshiro T, Mukai K, Kosaki G. Prevention of hemoglobinuria by administration of haptoglobin. *Res Exp Med (Berl).* 1980;177:1-12
- Suzukawa K, Ninomiya H, Mitsuhashi S, Anno I, Nagasawa T, Abe T. Demonstration of the deposition of hemosiderin in the kidneys of patients with paroxysmal nocturnal hemoglobinuria by magnetic resonance imaging. *Intern Med.* 1993;32:686-690

Can an Alternative Umbilical Arterial Catheter Solution and Flush Regimen Decrease Iatrogenic Hemolysis While Enhancing Nutrition? A Double-Blind, Randomized, Clinical Trial Comparing an Isotonic Amino Acid With a Hypotonic Salt Infusion

Jodi K. Jackson, Deborah J. Biondo, Janice M. Jones, Pamala J. Moor, Stephen D. Simon, Robert T. Hall and Howard W. Kilbride

Pediatrics 2004;114:377-383

DOI: 10.1542/peds.114.2.377

**Updated Information
& Services**

including high-resolution figures, can be found at:
<http://www.pediatrics.org/cgi/content/full/114/2/377>

References

This article cites 25 articles, 7 of which you can access for free at:
<http://www.pediatrics.org/cgi/content/full/114/2/377#BIBL>

Citations

This article has been cited by 1 HighWire-hosted articles:
<http://www.pediatrics.org/cgi/content/full/114/2/377#otherarticles>

**Post-Publication
Peer Reviews (P³Rs)**

One P³R has been posted to this article:
<http://www.pediatrics.org/cgi/eletters/114/2/377>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Nutrition & Metabolism
http://www.pediatrics.org/cgi/collection/nutrition_and_metabolism

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.pediatrics.org/misc/Permissions.shtml>

Reprints

Information about ordering reprints can be found online:
<http://www.pediatrics.org/misc/reprints.shtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

