

## JOURNAL CLUB

# Sucking Improvement Following Blood Transfusion for Anemia of Prematurity

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**Objective:** To determine whether correction of anemia of prematurity by packed red blood cell transfusion improves sucking.

**Design:** Nonexperimental intervention study.

**Setting:** Neonatal intensive care unit of Shaare Zedek Medical Center, Jerusalem, Israel, between July 23, 2006, and December 16, 2007.

**Patients:** Thirty-six neonates at a gestational age of 34 weeks or younger, feeding orally, who developed anemia of prematurity.

**Intervention:** Packed red blood cell transfusion, 15 mL/kg.

**Main Outcome Measures:** Change in sucking parameters recorded with the Kron Nutritive Sucking Apparatus for 5 minutes and ingested volume, prior to and 1 to 2 days after intervention.

**Results:** The mean (SD) gestational age was 30.1 (2.1) weeks, and the mean (SD) birth weight was 1436 (45) g. At the time of the study, the mean (SD) postnatal age was 46 (26) days, the mean (SD) weight was 2311 (36)

g, and the mean (SD) hematocrit was 26.7% (2.6%). Overall, there was no change in the number of sucks, number of bursts, or maximum negative pressure generated. Daily weight gain increased after transfusion (mean [SD] weight gain, 30.9 [10.0] g before transfusion vs 36.5 [13.0] g after transfusion;  $P = .02$ ). The babies were then stratified into those below the median number of sucks (109 sucks) before transfusion (poor feeders) and those at or above the median (better feeders). In the former subgroup only, changes from before transfusion to after transfusion were found in the number of sucks (mean [SD] sucks, 73.4 [29.5] vs 108.9 [53.3], respectively;  $P = .006$ ; mean [SD] sucks per burst, 3.4 [1.4] vs 4.9 [2.8], respectively;  $P = .01$ ) and volume consumed (mean [SD] volume, 17.1 [9.8] mL vs 23.2 [12.8] mL, respectively;  $P = .004$ ).

**Conclusions:** Correction of anemia of prematurity with blood transfusion improved sucking and volume ingested in premature infants who were poor feeders prior to the transfusion. It also enhanced overall weight gain.

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**T**RADITIONAL MANIFESTATIONS of symptomatic anemia of prematurity (AOP) include pallor, lethargy, decreased activity, tachypnea, tachycardia, apnea or bradycardia, and poor weight gain associated with poor feeding.<sup>1,2</sup> Anemia of prematurity is frequently blamed for impairing feeding and weight gain because of diversion of tissue oxygen delivery and energy supplies to other vital body functions.<sup>3</sup>



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Oral feeding of premature infants is a complex process requiring coordination of sucking, swallowing, and breathing to facilitate feeding while avoiding aspira-

tion into the airways.<sup>4</sup> Sucking activity involves the integration of multiple central nervous system sensory and motor functions.<sup>5</sup> To express milk, the newborn must

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produce negative intraoral pressure simultaneous with compression of the nipple between the tongue and hard palate in a rhythmic fashion.<sup>6</sup> Nutritive sucking is organized in a series of sucking bursts interspersed with pauses at a rate about half that of nonnutritive sucking bursts.<sup>7</sup> Although sucking in the fetus appears as early as postmenstrual age 15 to 18 weeks,<sup>8</sup> at this stage there is little coordination between the sucking and swallowing processes. By postmenstrual age 32 to 34 weeks, sucking matures sufficiently to

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be coordinated with swallowing, and at this corrected age premature babies should be able to achieve effective oral feeding.<sup>9</sup> The frequency, the maximal negative pressure of sucks, and the duration of the sucking bursts increase in parallel with advancing postmenstrual age as a result of developing neurologic mechanisms of the maturational processes involved in feeding.<sup>6,10</sup>

We hypothesized that correction of AOP with packed red blood cell transfusion would be associated with an improved sucking pattern and, as a secondary outcome, increased weight gain. We measured sucking patterns in anemic premature infants prior and subsequent to a blood transfusion, using a computerized tool specifically designed for this purpose.<sup>11,12</sup>

## METHODS

### SUBJECTS

A convenience sample of infants born at less than 34 weeks' gestation at Shaare Zedek Medical Center, Jerusalem, Israel, who developed AOP, were on full enteral feeding, and were receiving all or most of their feedings orally for at least 4 days prior to packed red blood cell transfusion were eligible for the study. Exclusion criteria were anemia associated with conditions including sepsis or acute hemolysis, intraventricular hemorrhage grade 3 or 4, periventricular leukomalacia, and major congenital malformations, especially those affecting the oral cavity or pharynx. The study received institutional review board approval at the Shaare Zedek Medical Center. Signed, informed parental consent was obtained prior to enrollment.

### SUCKING MEASUREMENTS

For the study measurements, infants were fed either infant formula or expressed breast milk. Five-minute records, commencing at the beginning of a routine feeding (3 hours after initiation of the previous feeding), were collected with a specially designed device. Infants were picked up, swaddled, and brought to a quiet alert state before sucking measurements were performed. After the measurement was completed, the infants continued their routine breastfeeding or bottle feeding.

The infant feeding device is a modification of the Kron Nutritive Sucking Apparatus<sup>11,12</sup> and comprises a pressure transducer embedded into a block, which is attached to a single-holed standard infant feeding nipple on one side and to a standard bottle on the other (**Figure**). The sucking process generates analog signals, which are transformed into digital signals by Biopac MP150 hardware and AcqKnowledge version 3.8.1 software systems (Biopac Systems, Inc). Specially designed software was used to analyze the varying pressure of sucks using temporal and pressure threshold criteria, which distinguished true sucks from movements or other artifacts. The following sucking variables were measured: total number of sucks, total number of bursts, and maximum negative sucking pressure. The average number of sucks per burst, average suck duration, and average burst duration were calculated from these parameters.

Infants whose number of sucks was less than 20 during the 5 minutes of the first measurement were removed from the study as we have previously observed that this low number of sucks may be caused by stiffness of the nipple used and may result in artifacts.

The software produces a summary of each participant's sucking parameters translated into an Excel file (Microsoft Corp).



**Figure.** Sucking device. The block with the built-in transducer is inserted between the bottle and the nipple. The cable connects to the digitalizer.

The mean and standard deviation of each of the sucking measurements over 5 minutes were calculated, and the volume ingested was recorded.

### WEIGHT GAIN

Routine infants' weight measurements were recorded for the 7 days before and the 7 days after the transfusion. The mean average daily weight gain for each period was calculated.

### PROTOCOL

The following were used as indications for blood transfusion in infants with AOP: (1) capillary hematocrit 27% or lower in newborns not requiring supplemental oxygen; or (2) capillary hematocrit 35% or lower for those requiring supplemental oxygen. Prior to packed red blood cell transfusion, complete blood cell counts including a reticulocyte count were obtained. Sucking parameters were measured as described earlier prior to transfusion of 15 mL of packed red blood cells per 1 kg. A new hematocrit determination was performed 24 to 48 hours after completion of the transfusion. Sucking parameters were then measured a second time. In the event that the hematocrit value did not increase by 20% over baseline, the baby was removed from the study. Subsequent nursery care was routine.

### STATISTICAL ANALYSIS

The primary outcome of the study was the number of sucks recorded during the measurement period. Additional sucking parameters as well as ingested volume and average daily weight gain were secondary outcomes of the study. Assuming an initial mean (SD) of 147 (70) sucks and an increase of 32 sucks based on the expected difference in the number of sucks (primary outcome) before and after the correction of AOP, with  $\alpha = 5\%$  (1-way) and power of 80%, a sample size estimate of 30

**Table 1. Demographic and Feeding Features of 36 Infants**

Variable	Value
Continuous, mean (SD)	
Gestational age, wk	30.1 (2.1)
Birth weight, g	1436 (45)
Postnatal age, d	46 (26)
Weight, g	2311 (36)
Hematocrit, %	26.7 (2.6)
Categorical, No. (%)	
Male	23 (63.9)
Type of feeding	
Bottle only	24 (66.7)
Breastfeeding only	1 (2.8)
Breastfeeding and bottle	11 (30.6)
Feeding modality	
Oral	26 (72.2)
Mixed, oral and gavage	10 (27.7)
Oxygen supplementation	6 (16.7)

**Table 2. Comparison of Sucking Parameters and Average Daily Weight Gain Before and After Transfusion in 36 Infants**

Parameter	Mean (SD)		P Value
	Before Transfusion	After Transfusion	
Sucks, No.	108.5 (52.3)	116.4 (50.4)	.41
Bursts, No.	23.2 (8.5)	22.6 (7.5)	.71
Sucks/burst, No.	4.7 (2.0)	5.2 (2.5)	.16
Suck duration, s	0.45 (0.13)	0.45 (0.11)	.80
Burst duration, s	9.3 (5.1)	8.4 (3.5)	.35
Pmax, cm H <sub>2</sub> O	51.9 (15.9)	54.6 (21.0)	.39
Ingested volume, mL	16.8 (11.8)	19.1 (12.8)	.22
Mean daily weight gain, g	30.9 (10.0)	36.5 (13.0)	.02

Abbreviation: Pmax, average maximal sucking negative pressure.

babies was calculated.<sup>4</sup> Categorical values were compared using Fisher exact test. Continuous values were evaluated using *t* test for demographic and baseline comparisons, while paired *t* test was used for comparing individual infants' measurements over the study period.

## RESULTS

Thirty-nine infants were enrolled in the study between July 23, 2006, and December 16, 2007. One infant was excluded because of a change in formula between the first and second measurements, which may have confounded the second reading, and 2 others were excluded owing to a low number of sucks recorded during the first measurement. Demographic data of the 36 infants who completed the study are depicted in **Table 1**.

### SUCKING PARAMETERS

Overall, there were no significant differences in the number of sucks or other sucking parameters between the first and second measurements (**Table 2**). No significant changes were observed in the amount of nutrient the babies ingested during the 5 minutes of the measurement

**Table 3. Demographic Features of Subgroups Based on Median Number of Sucks Before Correction of Anemia of Prematurity**

Variable	<109 Sucks (n = 18)	≥109 Sucks (n = 18)	P Value
Categorical, No. (%)			
Male	10 (55.6)	13 (72.2)	.49
Feeding modality			
Oral	12 (66.7)	14 (77.8)	.71
Mixed, oral and gavage	6 (33.3)	4 (22.2)	.71
Oxygen supplementation	2 (11.1)	4 (22.2)	.42
Continuous, mean (SD)			
Gestational age, wk	30.8 (1.6)	29.2 (2.8)	.09
Postmenstrual age, wk	36.6 (3.0)	36.6 (1.7)	.50
Birth weight, g	1530 (470)	1350 (420)	.23
Weight, g	2330 (380)	2290 (340)	.71
Daily weight gain, g	31.6 (10.3)	30.9 (10.6)	.84
Hematocrit, %	26.4 (1.9)	27.1 (3.2)	.49
Ingested volume, mL	17.1 (9.8)	16.4 (13.8)	.49
Time between measurements, h	32.8 (13.5)	26.2 (6.3)	.08

before and after correction of AOP. In contrast, we did find a statistically significant increase in average daily weight gain during the week subsequent to the correction of AOP compared with weight gain during the prior week.

Ten infants who required gavage feeding to complete their feeds were also analyzed separately. In keeping with the entire group, no significant change in any of the parameters was observed between measurements.

Separate analysis was also performed for a group of 6 infants who were receiving supplemental oxygen at the time of transfusion. There was a trend to an increased number of sucks between measurements, but this did not reach statistical significance ( $P = .06$ ). All other measured parameters showed no significant changes.

### STRATIFICATION BY QUALITY OF SUCKING

Because of the possibility that correction of AOP translated into improved sucking only in infants in whom sucking was already impaired at baseline, we divided the subjects into 2 subgroups: those with an initial median of fewer than 109 sucks (poor feeders) and those with an initial median of 109 or more sucks (better feeders). Demographic characteristics of the 2 subgroups were not significantly different (**Table 3**). In the better feeders, there were no significant differences between the first and second sucking measurements or in the volume of milk consumed. In the poor feeders, however, both the number of sucks and the sucks per burst were improved following the blood transfusion (**Table 4**). In addition, there was an increase in ingested volume in this subgroup between the first and second measurements.

**Table 4. Comparison of Sucking Parameters Over 5 Minutes Before and 24 to 48 Hours After Blood Transfusion Within Groups**

Sucking Parameter	Mean (SD)		P Value
	Before Transfusion	24-48 h After Transfusion	
Poor feeders (n = 18)			
Sucks, No.	73.4 (29.5)	108.9 (53.3)	.006
Bursts, No.	21.7 (7.7)	23.6 (7.5)	.58
Sucks/burst, No.	3.4 (1.4)	4.9 (2.8)	.01
Suck width, s	0.44 (0.17)	0.44 (0.09)	>.99
Burst width, s	11.6 (5.9)	9.6 (4.2)	.24
Pmax, cm H <sub>2</sub> O	50.5 (21.9)	59.1 (21.9)	.09
Ingested volume, mL	17.1 (9.8)	23.2 (12.8)	.004
Better feeders (n = 18)			
Sucks, No.	143.5 (46.4)	123.8 (47.6)	.12
Bursts, No.	24.8 (9.2)	22.1 (7.7)	.31
Sucks/burst, No.	5.9 (1.8)	5.6 (2.0)	.59
Suck width, s	0.47 (0.07)	0.46 (0.13)	.68
Burst width, s	7.1 (2.9)	7.3 (2.4)	.72
Pmax, cm H <sub>2</sub> O	53.2 (13.7)	50.2 (19.7)	.43
Ingested volume, mL	16.5 (14.0)	15.0 (12.0)	.64

Abbreviation: Pmax, average maximal sucking negative pressure.

### COMMENT

Effective, nutritive sucking reflects the culminative interaction of several physiological processes, most notably muscle tone and strength, as well as neurologic maturation of the suck-swallow mechanism.<sup>13</sup> Weak sucking in premature babies has been associated with poor generalized muscle tone and strength.<sup>14-16</sup> Sucking requires integrity of the cranial nerves to innervate the responsible muscles.<sup>17</sup> The premature infant exerts a great deal of effort and energy in oral feeding. At this stage, sucking and swallowing frequently result in feeding-associated apnea and decreased oxygen saturation.<sup>18,19</sup> Anemia may further exacerbate the situation, compromising the increased effort required for effective sucking and swallowing. It therefore seemed logical that correction of AOP would be beneficial with regard to sucking ability. However, as blood transfusions are not free of complications,<sup>20,21</sup> the decision to correct or not correct AOP should be based on specific criteria.

Overall, we found no significant change in sucking parameters in babies with AOP prior to and after correction of the AOP. However, in the subgroup of infants who did have poor sucking at baseline, there was a significant improvement in both sucking parameters and volume ingested. The fact that these changes occurred only in the poor feeders suggests that the most probable mechanism for the increase in the feeding amount was the increase in the number of sucks.

The transfusion of packed red blood cells may have contributed significantly to this improvement. In contrast, in those infants who were better suckers prior to the transfusion, it is possible that impaired sucking was not a clinical manifestation of their AOP and as a result no change in sucking pattern was associated with correction of their AOP. Improvement in sucking following correction of AOP was apparent only in the sub-

group of infants whose sucking at baseline was already poor.

Previous studies by Medoff-Cooper et al<sup>10,14</sup> and Bu'Lock et al<sup>22</sup> have shown that the sucking mechanism of premature infants undergoes maturation during the first weeks of life. It could therefore be argued that the improved sucking demonstrated in 1 subgroup was due to a physiological maturation process. If so, improvement should have been noted in all infants, including those with more effective sucking at baseline. Although the interval between measurements was slightly longer in the poor feeders, the difference was neither statistically nor clinically significant. The improvement we did find in the poor feeders therefore cannot be attributed to spontaneous maturation.

There are some possible limitations to the study. Although we showed an association between an increase of hemoglobin levels and sucking improvement, to our knowledge no formal investigation has been conducted to establish whether a correlation exists between hemoglobin levels and suckling abilities prior to correction of AOP. It is possible that there is a learning curve and that some infants who sucked poorly on the first measurement improved by the second. If this were the case, however, the improved sucking would not have been limited to those who were poor suckers at baseline. Because of administrative and logistical issues related to ordering the blood and its arrival in the nursery from the blood bank, the daily timing of the sucking measurements could not be standardized. The statistical phenomenon of regression toward the mean (meaning that infants with the extreme values of number of sucks at the first measurement may have approached the mean at the second measurement) may have influenced the results after stratification into subgroups dependent on the median number of sucks.<sup>23</sup> On the other hand, as there was a significant difference in the number of sucks between measurements ( $P = .006$ ) only in the poor feeders, it seems unlikely that this phenomenon acted as a confounding feature in the interpretation of our results. Finally, as we did not study nonanemic or anemic but non-transfused matched infant counterparts, we could not accurately isolate the individual effects of maturation, anemia, and transfusion on sucking.

### CONCLUSIONS

Correction of AOP improved feeding patterns and the volume of food ingested in premature babies whose feeding patterns prior to AOP correction were already compromised. Weight gain was significantly improved in the entire group during the week following correction of AOP compared with the week prior to the transfusion. Poor feeding and failure to gain weight may be considered as adjuncts to hematological parameters in the decision-making process as to whether to transfuse premature infants for AOP, although further data should be obtained to support this concept.

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## Correction

**Errors in Text and Conversion Factors.** In the Article titled "Validation and Refinement of a Prediction Rule to Identify Children at Low Risk for Acute Appendicitis" by Kharbanda et al, published in the August issue of the Archives (2012;166[8]:738-744), errors occurred in the text and in conversion factors given in the text, 3 table footnotes, and 2 figure legends. In the text, on page 739, the last sentence in the right-hand column (which continues onto page 740) should have read: "The following variables were entered: duration of abdominal pain, nausea, emesis, history of focal RLQ pain, presence of abdominal tenderness, maximal tenderness in the RLQ, abdominal pain with walking, abdominal pain on the right side with walking, and the absolute neutrophil and white blood cell counts using both continuous and categorical cutoff points." Also on page 739, the first sentence of the "Data Analysis" subsection should have read as follows: "The previously published low-risk prediction rule consisted of the following variables: absolute neutrophil count of  $6.75 \times 10^9/\mu\text{L}$  or less (to convert the count to  $\times 10^9$  per liter, multiply by 1), absence of nausea, and absence of maximal tenderness in the right lower quadrant (RLQ) of the abdomen." On page 741, the second footnote to Table 1 should have appeared as: "SI conversion factor: To convert WBC count to  $\times 10^9$  per liter, multiply by 1." On pages 741 and 742, the second footnote to Tables 3 and 4 should have appeared as: "SI conversion factor: To convert ANC to  $\times 10^9$  per liter, multiply by 1." Also on those pages, the second sentence of the legends to Figures 2 and 3 should have read: "ANC indicates absolute neutrophil count (to convert count to  $\times 10^9$  per liter, multiply by 1); RLQ, right lower quadrant."