Original Article

Efficacy and safety of parenteral nutrition with iron sucrose for anemia prevention in preterm infants: A randomized, double-blind controlled study

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Background and Objectives: Our objective is to study the efficacy and safety of parenteral nutrition (PN) with iron sucrose to prevent anemia in preterm infants. **Methods and Study Design:** We performed a randomized, double-blind controlled trial in which preterm infants were divided into five groups randomly: a control group (PN without iron sucrose, namely group Iron-0), and intervention groups (PN with iron sucrose 100 μg/kg/d, 200 μg/kg/d, 300 μg/kg/d and 400 μg/kg/d, namely group Iron-1, 2, 3, and 4, respectively). The indicators were red blood cell (RBC) parameters, iron storage and oxidant stress. **Results:** One hundred infants completed this study. Excepting the RBC count in Iron-2, the value of erythrocyte parameters in intervention groups decreased less than that in the control group. And the decrease of RBC count in Iron-1 (-0.6×10^{12}/L vs -0.9×10^{12}/L, p=0.033), hemoglobin in Iron-4 (-26.0 g/L vs -41.0 g/L, p=0.03) and hematocrit in Iron-1(-9.5% vs -14.0%, p=0.014) was significantly less than in the control group. The change of ferritin in Iron-4 was significantly higher than in the control group (280 ng/ml vs 118 ng/ml, p=0.04). There was no difference in serum iron in intervention groups when compared to the control group (p>0.05). Except for the change of malondialdehyde (MDA) in Iron-1, the increase in other intervention groups was higher than in the control group (p>0.05). **Conclusions:** PN with iron sucrose for prevention of anemia in preterm infants is safe and efficacious to some extent.

Key Words: preterm infants, anemia, iron sucrose, parenteral nutrition

INTRODUCTION

Preterm infants are prone to have iron deficiency anemia (IDA) because of a shortage of iron, a short half-life erythrocyte, and catch-up growth.[1] The incidence of iron deficiency (ID) in infants with a gestational age <32 weeks or birth weight <1,500 g is 25% to 85%.[2] The oral route, intramuscular injections, and intravenous infusions are often used to administer iron. However, preterm infant's incomplete development of the digestive tract causes poor iron absorption, and muscle injections are painful. Therefore, the intravenous method is a good choice for iron supplementation.

Parenteral nutrition (PN) is often used during the first day after birth to sustain life in preterm infants. Yet iron is not routinely added to PN in China. In recent years, many studies have focused on delayed umbilical cord ligation and umbilical cord squeezing.[3,4] The results have showed that some of the remaining blood in the placenta can flow to the newborn through placental blood transfusion, so preterm infants receive an "iron supplement" at birth. In our previous study,[5] we found the physical and chemical properties of the PN containing different doses (0, 0.25, 0.5, 0.75, 1 mg/100 mL) of iron sucrose were stable. Therefore, in this study, PN was used as a carrier to supplement iron on an infant's first day after birth. This

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Manuscript received 06 September 2021. Initial review completed 08 November 2021. Revision accepted 12 March 2022.
doi: 10.6133/apjcn.202206_31(2).0008

study focused on the efficiency and safety of PN with iron sucrose to prevent anemia in preterm infants.

METHODS

Patients

We recruited 130 preterm infants admitted to the NICU within 24 hours after birth in Xinhua Hospital in this study. The recruitment standards were preterm infants (gestation age <37 weeks), low birth weight (more than 1,500 g and less than 2,000 g) and a duration of PN of more than 7 days. The exclusion standards were had accepted PN before recruitment, abnormal liver and/or kidney function, hemolytic disease, blood transfusion during the trial, and severe congenital malformations. The recruited infants were divided randomly into five groups. The control group was designated as Iron-0 and received PN without iron sucrose. The intervention groups were Iron-1 (PN with 100 μg/kg/d iron sucrose), Iron-2 (PN with 200 μg/kg/d iron sucrose), Iron-3 (PN with 300 μg/kg/d iron sucrose), and Iron-4 (PN with 400 μg/kg/d iron sucrose). The study was approved by the Ethics Committee of Xinhua Hospital. The trial registration number is NCT02743572.

The Preparation of PN

The iron sucrose (Venofer®, American Regent, Inc., Verlove, Switzerland, 100 mg iron/5 ml) was diluted in normal saline to a concentration of 2 mg iron sucrose/1 ml saline. According to the order of the infant enrolled, we added different dosages of iron to PN. The PN was prescribed by clinicians on the basis of weight, volume of enteral nutrition, and day of birth.

Nutritional drugs and materials

The following were used to prepare the PN with iron sucrose: 20% MCT/LCT (Germany, B. Braun Melsungen AG), 10%, 25%, and 50% glucose for injection (American Baxter), 6% pediatric amino acid (Shanghai Long March Fuji Pharmaceutical Co. LTD), a water-soluble vitamin for injection, a fat-soluble vitamin for injection (II) (Sino-Swed Pharmaceutical Co. LTD), 10% kalium chloride and 10% calcium gluconate (Shanghai Xinyi Jinhe Pharmaceutical Co. LTD), 10% sodium chloride and 25% magnesium sulphate for injection (Shanghai Xudonghaipu Pharmaceutical Co. LTD), iron sucrose for injection, and a parenteral nutrition infusion bag (PVC, Taiwan Tono Medical Equipment Co. LTD).

Diagnosis of anemia

The hemoglobin is less than 164 g/l, 160 g/l, 135 g/l, and 107 g/l at birth, one week after birth, three weeks after birth, and six weeks after birth, respectively.[6]

General data

The general information (sex, gestational age, birth weight), duration of PN, ant the times when blood was drawn from a capillary or vein were recorded.

Laboratory indices

Anemia indices

The red blood cell count (RBC), hemoglobin (Hb), and hematocrit (HCT) were tested before and after PN. These indices were tested by the XS-500I automatic hematology analyzer.

Iron-related parameters

Serum ferritin (SF) and serum iron (SI) were tested before and after PN. SF was measured by an enzyme-linked immunosorbent assay (ELISA) using a Crystal Ferritin LEISA Kit 96-well. SI was measured by colorimetry.

Oxidant stress indices

Malondialdehyde (MDA) were tested before and after PN. This index was tested by ELISA using a Nanjing Jiancheng 96-well kit.

Infection indices

White blood cell count and c-reactive protein were tested before and after PN. The measurement of the infection indices is the same as the measurement of anemia indices.

Statistics

The data was analyzed with SPSS 21.0. The measurements of normal distribution data are expressed as mean±SD, while abnormal distribution data are characterized by P50 (P25, P75). We used an ANOVA or Mann-Whitney U test to compare the differences in the measurement data among the groups. Count data are expressed as percents, and the χ^2 test was used to compare data among the five groups. $p<0.05$ was considered statistically significant.

RESULTS

General

One hundred preterm infants completed the study: 20 belonged to the Iron-0 group; 17 belonged to the Iron-1 group; 21 belonged to the Iron-2 group; 23 belonged to the Iron-3 group; and 19 belonged to the Iron-4 group. Twenty-nine infants were excluded: 6 had a transfusion; 1 died because of pneumorrhagia; and 22 had no complete data. There was no statistically significant difference regarding sex, gestation age, birth weight, duration of PN, and the times for drawing blood from a capillary or vein among the five groups ($p>0.05$) (Table 1).

Erythrocyte parameters and anemia

Before PN, there was no significant difference in RBC, Hb, and HCT among the control and intervention groups ($p>0.05$) (Table 2). The incidence of anemia among the five groups was 15.0%, 17.6%, 4.8%, 13.0%, and 5.3%, respectively ($\chi^2=2.71$, $p=0.187$).

After PN, the value of RBC and HCT in Iron-1 group was significantly higher than in the control group ($p<0.05$). The values of other RBC, Hb, and HCT in the intervention groups had an upward tendency compared with the control group, but there was no significant difference ($p>0.05$) (Table 2). The incidence of anemia among the five groups was 55.0%, 47.0%, 57.1%, 52.2%, and 42.1%, respectively ($\chi^2=1.17$, $p=0.884$).

The value of RBC and HCT in Iron-1 and Hb in Iron-4 decreased significantly less than in the control group ($p<0.05$). Except for the RBC in the Iron-2 group, which was decreased slightly more than in the control group, the extent of the decrease of the other erythrocyte parameters

Table 1. General data of preterm infants among five groups[†]

	Iron-0	Iron-1	Iron-2	Iron-3	Iron-4	*p* value
N	20	17	21	23	19	
Sex (male: female)	10/10	8/9	12/9	10/13	10/9	0.921
Gestation, week	33.3±2.2	33.2±1.5	33.2±2.1	33.1±2.0	33.1±2.1	0.964
Birth weight, g	1790±125	1737±193	1731±162	1807±127	1758±146	0.409
During of PN, day	16.3±5.7	12.9±4.8	16.3±4.7	14.4±5.7	14.3±3.9	0.193
The times of drawing blood from capillary, time	10 (6, 16)	7 (3, 12.5)	8 (6, 15.5)	7 (4, 10)	7 (6, 11)	0.346
The times of drawing blood from vein, time	4 (3, 3.8)	4 (3, 4.5)	4 (2.5, 5)	3 (2, 4)	3 (2, 5)	0.558

N: Number; PN: Parenteral Nutrition.
[†]Normal distribution data was expressed as mean±SD, and abnormal distribution data was media (P25, P75).

Table 2. Comparison of reticulocyte parameters in five groups before and after PN with iron

Group	Before PN	After PN	Δ	*p*1	*p*2	*p*3
RBC, 10^{12}/L						
Iron-0	4.7±0.5	3.7±0.4	-0.9 (-1.4, -0.6)	-	-	-
Iron-1	4.7±0.6	4.1±0.7	-0.6 (-0.9, -0.3)	0.923	0.042	0.033
Iron-2	4.6±0.5	3.9±0.6	-1.0 (-1.3, -0.2)	0.803	0.166	0.449
Iron-3	4.6 ± 0.4	3.9±0.7	-0.7 (-1.1, -0.4)	0.711	0.222	0.184
Iron-4	4.6±0.5	4.0±0.7	-0.7 (-1.1, -0.3)	0.562	0.109	0.065
HB, g/L						
Iron-0	180±19	132±19	-41.0 (-64.3, -34.0)	-	-	-
Iron-1	174±23	142±24	-35.0 (-47.0, -17.0)	0.361	0.170	0.056
Iron-2	177±19	136±22	-41.0 (-60.0, -20.0)	0.601	0.513	0.434
Iron-3	176±18	140±25	-36.0 (-54.0, -25.0)	0.453	0.229	0.128
Iron-4	170±21	140±25	-26.0 (-51.0, -20.0)	0.184	0.275	0.030
HCT, %						
Iron-0	51.0±4.5	36.7±5.1	-14.0 (-19.0, -4.9)	-	-	-
Iron-1	50.8±6.4	41.0±5.8[*]	-9.5 (-12.4, -7.5)	0.896	0.025	0.014
Iron-2	50.7±5.4	37.7±6.6	-12.9 (-12.6, -6.1)	0.827	0.600	0.584
Iron-3	50.9±4.4	39.0±7.0	-12.0 (-16.2, -7.7)	0.937	0.225	0.263
Iron-4	48.3±5.2	38.6±6.8	-9.9 (-16.2, -6.3)	0.165	0.342	0.054

RBC: red blood cell; HB: hemoglobin; HCT: hematocrit; Δ: rangeability of erythrocyte parameters after intervention; PN: Parenteral Nutrition.
Normal distribution data was expressed as mean±SD, and abnormal distribution data was media (P25, P75).
*p*1: compared the value in Iron 1 to 4 group to that in Iron-0 group before PN,
*p*2: compared the value in Iron 1 to 4 group to that in Iron-0 group after PN,
*p*3: compared the change of parameters in Iron 1 to 4 group to that in Iron-0 group after intervention.

in the intervention groups was lower than in the control group, but there was no significant difference (p>0.05) (Table 2).

Iron-related parameters

Before PN, there was no significant difference in SF or SI among control and intervention groups (p>0.05) (Table 3).

After PN, the SF significantly increased in the Iron-4 group when compared with the control group (p<0.05). The change of SF in Iron-4 also increased more than in the control group. The value of SI was higher in all intervention groups than in the control group, but there was no significant difference (p>0.05) (Table 3).

MDA

Before PN, there was no significant difference in MDA among the control and intervention groups (p>0.05).

The rangeability decreased in Iron-0 and Iron-1, and increased in Iron-2, Iron-3, and Iron-4, but there was no significant difference (p>0.05) (Table 4).

Infection

There were no differences in the infection incidence among the five groups before and after PN with iron sucrose (p>0.05) (Table 5).

DISCUSSION

Iron is an essential trace element in the human body and plays an important role in many cell functions and physical processes, including growth and development. Preterm infants have a high risk for iron deficiency or iron deficiency anemia because of the following reasons: 1) Approximately 60% of iron in the fetus is acquired during the third trimester of gestation, and the concentration of total iron, hemoglobin, serum iron, and storage iron in preterm infants is lower than in term infants.[7] 2) Because of rapid catch-up growth after birth, the preterm infants need high levels of iron. However, the iron they store can be consumed quickly during the first 6–8 weeks after birth. 3) The life span of erythrocytes in preterm newborns is short, approximately only 35–50 days. 4) Iatrogenic anemia may be induced by frequently drawing blood for laboratory tests.

It was found that incidences of anemia decreased in preterm infants who were given supplementary iron for 6 months after birth.[8] There are several methods to prevent IDA in preterm infants: supply iron during pregnancy; delay umbilical cord clamping after delivery; and supply iron for preterm infants by mouth, intramuscularly, or intravenously. This study focused on intravenous supplementary iron to prevent IDA in preterm infants. Intravenous iron preparations including iron sucrose, iron dextran, iron gluconate, and ferumoxytol were widely ac-

Table 3. Comparison of iron-related parameters in five groups before and after PN with iron

Group	Before PN	After PN	Δ	*p*1	*p*2	*p*3
SF, ng/ml						
Iron-0	135±803	253±134	118±143	-	-	-
Iron-1	119±70	164 (126, 206)	53.0 (13.3, 77.2)	0.583	0.339	0.312
Iron-2	182±173	364 ±231	183±247	0.332	0.115	0.378
Iron-3	133±75	182±56	49.2±64.1	0.941	0.146	0.106
Iron-4	163±123	443±281	280±266	0.453	0.017	0.040
SI, umol/L						
Iron-0	5.6±5.0	13.5±5.7	7.9±6.8	-	-	-
Iron-1	11.4±12.1	14.4±5.1	3.1 ±10.7	0.093	0.668	0.176
Iron-2	7.2±7.8	14.2±4.9	6.6±8.5	0.465	0.708	0.618
Iron-3	5.1±4.2	16.2±3.3	11.8±5.5	0.736	0.112	0.093
Iron-4	9.3±9.2	16.3±6.7	7.2±11.6	0.164	0.202	0.832

SF: serum ferritin; SI: serum iron; Δ: rangeability of erythrocyte parameters after intervention; PN: Parenteral Nutrition
Normal distribution data was expressed as mean±SD, and abnormal distribution data was media (P25, P75).
*p*1: compared the value in Iron 1 to 4 group to that in Iron-0 group before PN,
*p*2: compared the value in Iron 1 to 4 group to that in Iron-0 group after PN,
*p*3: compared the change of parameters in Iron 1 to 4 group to that in Iron-0 group after intervention.

Table 4. Comparison of MDA in five groups before and after PN with iron

Group	Before PN	After PN	Δ	*p*1	*p*2	*p*3
MDA, nmol/ml						
Iron-0	12.4 (8.6, 15.2)	15.8±12.4	-1.2±10.3	-	-	-
Iron-1	23.1±17.9	21.5±11.0	-1.6±19.6	0.095	0.213	0.957
Iron-2	15.2 (9.8, 17.0)	16.1±10.5	1.5 (-4.0, 6.8)	0.271	0.938	0.757
Iron-3	17.9±9.0	20.2±11.9	2.2±15.6	0.752	0.318	0.480
Iron-4	13.2±4.3	15.2±6.1	1.9±8.6	0.705	0.853	0.344

MDA: malondialdehyde; Δ: rangeability of erythrocyte parameters after intervention.; PN: Parenteral Nutrition
Normal distribution data was expressed as mean±SD, and abnormal distribution data was media (P25, P75).
*p*1: compared the value in Iron 1 to 4 group to that in Iron-0 group before PN,
*p*2: compared the value in Iron 1 to 4 group to that in Iron-0 group after PN,
*p*3: compared the change of parameters in Iron 1 to 4 group to that in Iron-0 group after intervention

Table 5. The indices of infection in preterm infants among five groups

	Iron-0	Iron-1	Iron-2	Iron-3	Iron-4	*p* value
Before PN						
CRP†	19/1	15/2	18/3	21/2	18/1	0.810
WBC‡	10.6 (8.6, 14.6)	10.1 (6.7, 12.6)	11.5 (7.2, 17. 5)	8.6 (7.4, 11.3)	7.2 (6.4, 10.7)	0.063
After PN						
CRP†	20/0	15/2	20/1	22/1	19/0	0.360
WBC‡	10.6 (8.2, 12.0)	10. 9 (9.8, 13.3)	11. 2 (8.9, 13.2)	10.9 (9.6, 14.3)	9.1 (6.7, 11.2)	0.078

WBC: white blood cell; CRP: c-reactive protein.
† number of normal CRP/number of abnormal CRP. CRP <8 mg/L is defined as normal level.
‡ $\times 10^9$/L

cepted in the world.[9,10] Previous studies tended to avoid suggesting administering iron dextran because the incidence of anaphylaxis with iron dextran was higher than with iron sucrose.[11] Therefore, iron sucrose was selected as intravenous supplementation for this study. The intestinal function of preterm infants in neonatal intensive care unit is immature, so they tend to have digestive intolerance and the amount of enteral nutrition cannot meet physiological needs. As a result, a high proportion of preterm infants used PN in the early stage after birth. This study took advantage of PN as a method to infuse iron sucrose, and we observed the indices of anemia, serum iron, ferritin and oxidative stress. But the duration of iron depended on the duration of PN. In this study, the average duration of PN was less than 3 weeks, which was the same for iron sucrose.

At present, providing preterm infants with dosages of intravenous iron is still controversial. The goal of nutrient intake in preterm infants is to narrow the gap between the intrauterine and extrauterine acquisition rate and help them to maintain a normal growth level. Based on this goal, a preterm infant would require an intravenous iron intake of 1.6–2.0 mg/kg/d or 5–6 mg/kg/d enterally. Because the enteral iron absorption rate is approximately 30%,[12,13] the demand for enteral iron is greater than for parenteral iron. Griffin and Cooke evaluated the iron demands in preterm infants who reach a birth weight of 1,000 g to 0.37 mg/kg/d at term,[14] and found the dosage is equal to 1.4–2.0 mg/kg/d from enteral intake (absorption rate is 20–37%).[15] However, these studies did not consider the blood loss and blood transfusion. The parenteral iron demand in very low birth weight infants is 0.20–0.27 mg/kg/d[14] and 0.20–4.00 mg/kg/d in infants whose birth weight is less than 3 kg.[16,17] The American Academy of Pediatrics recommends an enteral iron intake of 2 mg/kg/d for infants with birth weights between 1,500–2,500 g.[18] Considering this enteral iron recommendation, the low intestinal absorption rate, the close range between therapy dosage and toxic dosage, and the stability of PN, we selected 400 μg/kg/d of iron sucrose as the highest dosage, and a gradient dosage of 100 μg/kg/d.

Many studies recommended early supplementation with intravenous iron. Researchers found that supplementary iron at 2 weeks after birth can decrease the need for transfusion of very low birth weight infants when compared to starting at 6 to 8 weeks after birth.[19,20] Jin et al found by conducting a meta-analysis that supplementing iron early for low birth weight infants can reduce the range of decrease of Hb.[21] Joy et al researched 104 low birth weight infants: at 12-weeks, their Hb was significantly higher when starting to supplement iron 2 weeks rather than 6 weeks after birth.[22] The Hb values were 10.1±0.4 g/dL vs 9.2±0.4 g/dL. Friel et al randomized 26 very low birth weight infants (1–5 weeks of age) to provide them with either parenteral nutrition with iron dextran (0.20–0.25 mg/kg/d) or no iron.[23] There were no differences in Hb concentrations, the number of blood transfusions, growth development, or infection. In this study, all the recruited preterm infants started to receive PN with supplementary iron sucrose within 24 hours after birth. Although Hb cannot accurately reflect the iron status because of low specificity and sensitivity, it is, nonetheless a good way to evaluate the efficiency of IDA treatment. The range of decrease of the erythrocyte parameters among most preterm infants in the intervention groups was lower than in the control group. However, the range of decrease of RBC in the Iron-2 group was a slightly larger than the control group because of the following reasons: 1) The number of recruited infants in the study was small, and the variation range of the index within the group is a slightly larger, which may affect the outcomes. 2) The life span of RBC and the duration of PN were different among individuals, which lead to a difference in the amount of destroyed RBC by the end of PN.

SF is the main iron storage protein and tests for SF concentrations are widely used in clinic. A low level of SF occurs during the ID stage and ID progresses to IDA after iron stores depleted. Therefore, SF is the most sensitive for predicting and diagnosing IDA.[2] However, SF may also increase inflammation and infection. In our study, there were no differences in infection indices among the five groups before and after iron-containing PN.

SI is one of the most common indices for reflecting iron storage status. A study that researched the all-in-one PN with 200 μg/kg/d of iron sucrose for preterm infants found that the level of SI in the group that received iron sucrose was higher than in the group that did not receive iron sucrose after 2 weeks ($p>0.05$).[24] Our results showed that the SI level in preterm infants of most intervention groups was higher than in the control group after PN, indicating 100–400 μg/kg of iron sucrose per day in PN could improve infants' iron storage status.

Iron is not excreted from the human body, therefore, an excessive supply of iron may increase the risk of oxidative stress and growth retardation while interfering with the preterm infants' absorption and metabolism of other minerals. Furthermore, iron is a potential prooxidant, and iron overload may result in free oxygen-radicals-associated disorders. To evaluate indirectly the levels of

free radicals, unsaturated fatty acids (a primary product of lipid peroxidation) and MDA (a secondary product) are the indicators used. MDA is strongly cytotoxic because it can rapidly combine with proteins or nucleic acids.[25] A measurement of thiobarbituric acid reactive substances (TBARS) is widely used to evaluate lipid peroxidation. Unlike MDA, TBARS are not specific because other aldehydes and non-lipid materials may also react with thiobarbituric acid,[26] therefore, we chose MDA for this study to evaluate oxidative stress.

Grand et al studied the use of all-in-one PN with iron sucrose (1.5 mg/mL, 1 mg/kg) and found that MDA concentration at 24 hours after preparation was significantly higher than at 0 hour during storage (hour 0: 1555 [961; 1,903] nmol/L vs hour 24: 1,817 [1,216; 2,017] nmol/L; p=0.018).[27] Lipid peroxidation may occur quickly after the iron is added into PN solutions. In our study, the change in infants' MDA levels from the Iron-2, Iron-3, and Iron-4 group increased more than in the control group, but there was no significant difference.

One infant died and was excluded from the study. The infant experienced decreased oxygen saturation and a decreased heart rate suddenly on the sixth day after birth. A possible disseminated intravascular coagulation resulted in pneumorrhagia. The infant ultimately died because of respiratory and circulatory failure. There are no published reports about the effect of iron sucrose on the coagulation function. Therefore, we excluded the possibility that the death had resulted from infusing iron sucrose.

The shortcomings of this study are as follows: 1) The study only collected the number of capillary and vein punctures. We could not accurately record the blood volume drawn for laboratory tests. 2) Because of ethical issues, the testing of the erythrocyte parameters depended on clinical needs resulting in the different blood drawing time points before and after PN for each preterm infant. 3) Because the safe dosage of iron sucrose is not defined, the highest dosage in the study was set at 400 μg/kg/d iron sucrose. It follows we may not have reached to the optimal dosage of iron sucrose to prevent anemia in preterm infants. 4) The study focused on prevention, but because of the very high rate of loss from follow-up, we could not assess the incidence of anemia, over a longer time, in the study participants.

Conclusion

This study found that PN with iron sucrose of 100 to 400 μg/kg/d did not significantly increase the index of oxidant stress, and therefore, the PN could be safely administered to preterm infants. To a certain extent, PN with iron sucrose improved erythrocyte parameters and iron storage. However, the number of preterm infants in the study was small and parenteral iron sucrose of 400 μg/kg/d may not meet the infants' need for iron. We recommend further studies to test higher concentrations of iron sucrose to find the optimal dosage.

AUTHOR DISCLOSURES

Authors declare that they have no competing interests. This study received no funding.

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