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Comparison between Ferrous Ascorbate and Colloidal Iron in the Treatment of Iron Deficiency Anemia in Children from Kolkata, India

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Research Article

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ABSTRACT

Aim: To compare the efficacy and safety of ferrous ascorbate and colloidal iron in children with iron deficiency anemia.
Study Design: An open, randomized, comparative, parallel-group study.
Place and Duration of Study: Department of Pediatric Medicine of 'Nilratan Sircar Medical College and Hospital', Kolkata, India, between January 2009 and February 2010.
Methodology: Children between the age group of 6 months to 12 years were included if they had anemia defined as hemoglobin <10 gm%. Children received treatment with either ferrous ascorbate or colloidal iron for 12 weeks. Each child received elemental iron 3 mg/kg body weight/day. Follow-up assessments were performed at the end of week 4, week 8 and week 12.
Results: Out of the 137 children screened, 80 were included in the analysis. The mean rise in hemoglobin at the end of the 12 weeks was significantly higher in ferrous ascorbate group than colloidal iron group [3.24 ± 1.66 gm% vs. 1.42 ± 2.04 gm%; p <0.01]. Responder rate (hemoglobin ≥11.5 gm%) after 12 weeks of therapy was 53.57% in ferrous ascorbate group versus 10.34% in colloidal iron group; p<0.01.
Conclusion: The study provides evidence for the role of ferrous ascorbate as an efficient oral iron supplement in the treatment of iron deficiency anemia in children.

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Keywords: Anemia; children; hemoglobin; iron; ferrous ascorbate; colloidal iron.

1. INTRODUCTION

Children commonly develop anemia (low hemoglobin) after birth. Experimental and observational studies have linked iron deficiency (ID) with several adverse consequences of child development, including impairments in cognitive functions and motor development, growth, immune function, and increased risk of infection (Ojukwu et al., 2009). A recent study reported that behavior problems and low intelligence were significantly high among anemic children and that children with iron deficiency anemia (IDA) were more prone to having low attention and being hyperactive (Mubarak et al., 2010). IDA is one of the commonest nutrient deficiencies in India with a prevalence of about 75% in children under 5 years of age (Hanumante et al., 2008). Iron supplementation is the best available option to address ID and IDA in pregnant women and young children as it effectively increases intake of iron and, eventually, other anemia-related nutrients (Mora, 2002). Iron supplementation with different iron sources, has been recommended and used in many regions of the World for several years. More recently, the addition of other micronutrients to iron has been suggested (Rosado et al., 2010). The United Nations Children's Fund (UNICEF) recommends the utilization of an iron and folic acid supplement (UNICEF, UNU, WHO, 2001).

There are two general types of iron supplements which contain either the ferrous or ferric form of iron. In India, there are many marketed brands of liquid iron preparations available which contain iron salts/complexes like ferrous sulphate, ferrous fumarate, ferrous gluconate, ferric ammonium citrate, colloidal iron, ferrous ascorbate and ferric hydroxide polymaltose complex (also called Iron Polymaltose Complex or IPC) (Choudhury et al., 2011). In case of ferrous compounds [Fe(II) salts], at alkaline pH, Fe(II) is rapidly oxidized, resulting in the formation of large, non-absorbable ferric hydroxide polymers, which will attack the gut wall and produce a range of gastrointestinal symptoms and discomfort (Choudhry et al., 2007). Addition of ascorbic acid converts the ferric form to ferrous form thus making it absorbable from duodenum and upper jejunum, resulting in considerable enhancement of the absorption of iron. It has been demonstrated that Fe(II) ascorbate is less easily oxidized than Fe(II) in ferrous sulphate. Absorption of ferrous ascorbate averaged 52% higher than ferrous sulphate in subjects with ID. (Marx et al., 1982) Thus when administered as ferrous ascorbate, Fe(II) salt is more resistant to oxidation at alkaline pH, delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum GI adverse effects (Marx et al., 1982; Agarwal et al., 2006).

Several studies demonstrating the efficacy of ferrous ascorbate in the treatment of IDA have mainly concentrated on the adult population (Agarwal et al., 2006; HERS Study Group India., 2005; Guinea et al., 1996). The present study was undertaken considering the fact that there is no direct comparison demonstrating the efficacy of ferrous ascorbate and colloidal iron in pediatric age group. The aim of the present study was to evaluate and compare the efficacy of two marketed preparations of liquid iron (syrup) in India (one containing ferrous ascorbate and another containing colloidal iron) in children with IDA.

2. MATERIALS AND METHODS

The study (Study No: Zuv/Fern/Susp/1/2008) was carried out in the Department of Pediatric Medicine of 'Nilratan Sircar Medical College and Hospital', Kolkata, India. The study protocol was approved by the institutional ethics committee in January 2009. Study details and potential risks and benefits were explained to parents of each child, and written informed consent was obtained voluntarily from at least one of the parents before entering their child into the study.

2.1 Subject Eligibility

2.1.1 Inclusion criteria

Children between the age group of 6 months to 12 years were eligible if they had anemia defined as hemoglobin (Hb) less than 10 gm%. IDA diagnosis was based on the Guidelines by the British Society of Gastroenterology (Goddard et al., 2000) which included the combination of at least two of the following criteria in addition to Hb<10 gm% at baseline: lower than normal (80-100 fL) mean cell volume (MCV), raised red cell volume distribution (RDW) than the normal range [11 - 15%] or low serum ferritin levels (<12 ng/ml but not>100 ng/ml).

2.1.2 Exclusion criteria

The main exclusion criteria were: Anemia due to other causes than iron deficiency anemia, severe concurrent illness (cardiovascular, renal, and hepatic), known hypersensitivity to ferrous ascorbate or any other iron preparations, malignancy of any type, children with thalassemia major / aplastic or hypoplastic anemia, sickle cell anemia, hemolytic anemia or hemoglobinopathy and any other condition that in the opinion of the investigator did not justify the patient's inclusion.

2.2 Study Design

This was an open–label; randomized, comparative study for a duration of 12 weeks wherein treatment was assigned using a randomization code (generated using statistics software WINPEPI Version 8.6). Patients were assessed for the changes in the iron indices and adverse events at the time of enrollment and at the end of week 4, week 8 and week 12. During each visit the investigator performed the clinical examination of the child, following which a trained research assistant collected blood through peripheral venous puncture with disposable syringe. De-worming of the child was done as a part of routine procedure before entering the child into the study. A routine complete blood count (CBC) which includes the hemoglobin, hematocrit, red cell indices: the mean cell volume (MCV), mean cell hemoglobin (MCH) and mean concentration of hemoglobin per volume of red cells (MCHC), Red cell distribution width (RDW) and reticulocyte count was determined using Sysmex KX-21 cell counter at baseline (Day 0), week 4, week 8 and week 12. Serum ferritin was measured using Chemiluminescence Immunoassay (CLIA) at baseline and at week 12. Electrophoretic Pattern of Hemoglobin was determined using HPLC to detect abnormalities of hemoglobin in blood samples at the baseline.

2.3 Study Medication

The study medications used were "Feronia-XT Suspension" [Each 5ml containing ferrous ascorbate equivalent to Elemental Iron 30 mg & Folic acid 500 mcg; Manufactured by Zuventus Healthcare Ltd] and "Tonoferon Syrup" [Each 5 ml containing colloidal iron equivalent to Elemental Iron 80 mg, Folic acid 200 µg and Vitamin B12 2 µg; Manufactured by East India Pharmaceutical Works Limited]. The dosage of iron preparation was decided based on the body weight and each child received 3 mg/ kg body weight/ day of elemental iron. Though the two preparations differ slightly in their composition, the purpose of comparison was to get a glimpse of the practical usage of iron preparations in day to day practice of the physician.

2.4 Study Outcomes

Change in hemoglobin level at the end of each visit was set as the primary outcome of the study. The secondary outcomes included the change in hemoglobin levels based on the severity of anemia at baseline (moderate anemia corresponds to a level of 7.0-9.9 gm% while severe anemia corresponds to a level less than 7.0 gm%), changes in other iron indices, responder rate defined as the proportion of children becoming non-anemic [Hb≥ 11gm%] at the end of the study and incidence of any adverse events.

2.5 Statistical Analysis

All the statistically analyzed data are presented as mean ± standard deviation (SD) unless stated otherwise. The proportions of patients were reported as a percentage. Fisher's exact test was used to compare proportions, and t tests were used to compare means. Statistical significance was set for P value<0.05. The sample size calculation was done based upon superiority parallel design. Considering a desired power of 90%, allocation ration of 1:1, probability of Type I error of 5%, common SD for baseline of 2 gm% and the expected clinically relevant difference of 2 gm%, it was found that a minimum sample of 23 subjects in each arm was sufficient to provide statistically significant results.

3. RESULTS

Eligible subjects enrolled from January 2009 to November 2009. Baseline demographic data are tabulated in Table 1. A total of 137 patients were screened. Figure 1 shows the flow of patients for each visit during the study.

The change in iron indices during each visit with the study medications is tabulated in Table 2. The mean rise in Hb at the end of week 12 was 3.24 ± 1.66 gm% in ferrous ascorbate group (from 7.68 ± 1.50 gm% to 10.91 ± 1.63 gm%; p<0.01) while in colloidal iron group it was 1.42 ± 2.04 gm% (from 8.18 ± 1.60 gm% to 9.59 ± 1.55 gm%; p<0.01). The difference in the mean rise in Hb between the two groups was also found to statistically significant.

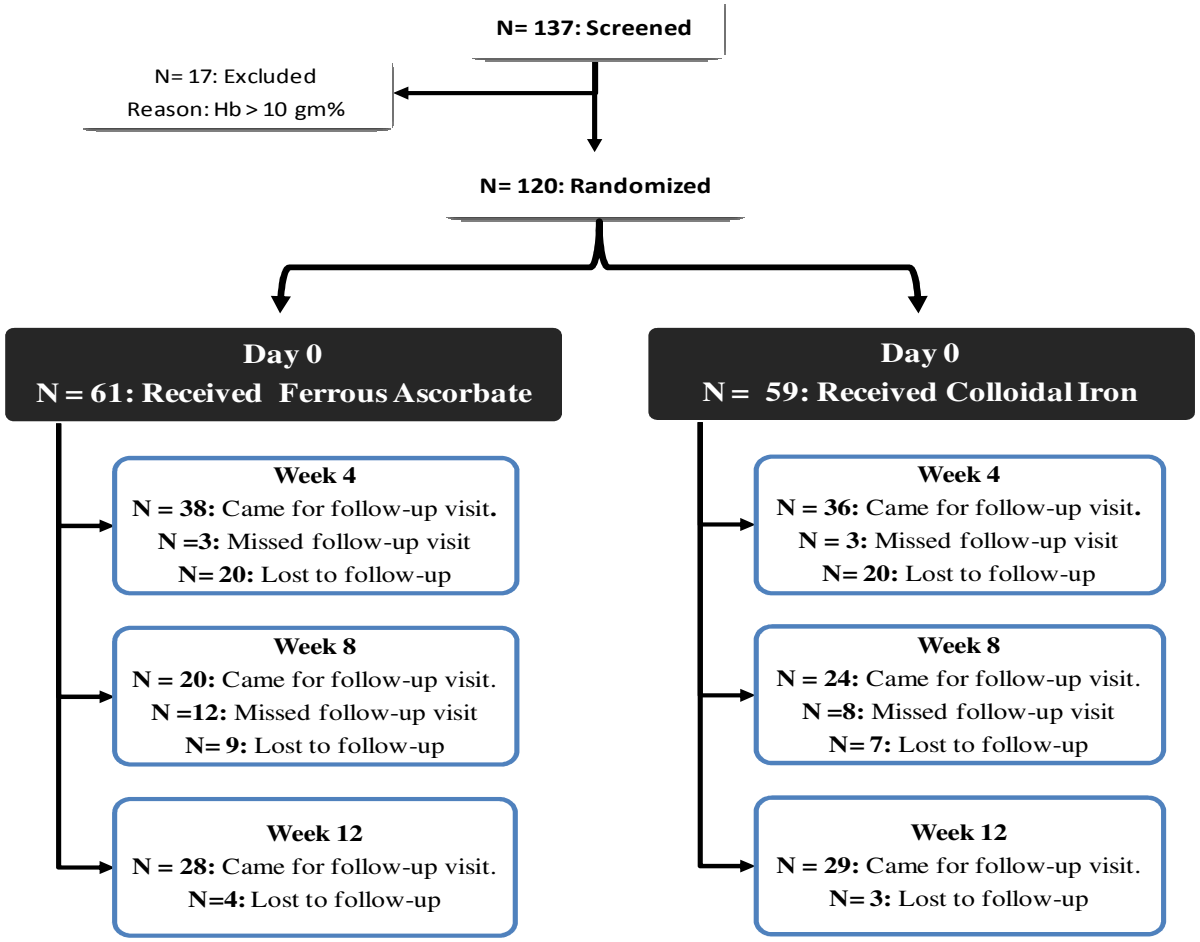

Figure 1. CONSORT flow diagram showing number of patients enrolled in the study, randomized to each treatment group and reasons for discontinuation.

At 12 weeks of therapy, the rise in serum ferritin level of ferrous ascorbate group was from 32.41 ± 22.75 ng/ml to 93.34 ±89.48 ng/ml; p<0.01 while that in colloidal iron group was from 32.33 ± 27.02 ng/ml to 49.31 ± 50.14 ng/ml; p = 0.12. The difference in the rise in ferritin level was higher in ferrous ascorbate group (60.93 ± 91.00 ng/ml versus 16.98 ± 54.65 ng/ml in colloidal iron group; p = 0.051).

Table 1. Baseline characteristics of the study population

n		**Ferrous ascorbate**	**Colloidal iron**
		41	39
Age (Years)	Mean ± SD	5.91 ± 3.73	4.37 ± 2.91
	Range	0.5 - 12	0.58 - 10
Age Distribution	< 2 years	24.39% (10/41)	35.89% (14/39)
	2 to 5 years	21.95% (9/41)	17.95% (7/39)
	> 5 to 12 years	53.65% (22/41)	46.15% (18/39)
Gender	Male	68.29% (28/41)	61.54% (24/39)
	Female	31.71% (13/41)	38.46% (15/39)
Severity of anemia*	Severe (Hb: < 7 gm %)	21.95% (9/41)	30.77% (12/39)
	Moderate (Hb: 7- < 10 gm %)	78.05% (32/41)	69.23% (27/39)
HbA_2 (%)	Mean ± SD	1.11 ± 0.31	1.11 ± 0.31
	Range	**1-2**	**1-2**

Subgroup analysis based on the severity of anemia is tabulated in Table 3. In children with severe as well as moderate anemia at baseline, there was a significant rise in mean Hb from baseline both the treatment groups. In children with moderate anemia at baseline, the difference in the mean rise in Hb in ferrous ascorbate was found to be significantly higher than colloidal iron after 12 weeks of therapy. A similar correlation was also observed in the responder rate (as shown in Table 3).

The proportion of children with higher rise in Hb [Hb>2 gm%] was observed in ferrous ascorbate group while in colloidal iron group, 41.4% of the treated children showed less than 1gm% rise in Hb. The distribution of children based on the rise in Hb after 12 weeks of therapy is shown in Figure 2.

Both the study medications were well accepted and no side-effects were observed.

Table 2. Effect on hematological parameters at each follow-up visit compared to baseline between the two treatment groups.

Parameters (Units)	Drug	N	Day 0	Week 4	N	Day 0	Week 8	N	Day 0	Week 12
Hb (gm%)	Fe Asc	25	7.53 ± 1.68	10.20 ± 1.01*†	24	7.74 ± 1.46	10.65 ± 1.16*†	37	7.78 ±1.62	11.38 ± 0.83*†
	C. Iron	22	7.68±2.18	9.35 ± 2.01*	21	8.21±1.18	9.73 ± 1.59*	29	7.49±1.88	9.92 ±1.83*
Hct (%)	Fe Asc	25	29.50± 5.23	34.07± 4.12*	25	30.41± 4.20	34.93± 4.71*	37	30.09±4.67	35.71± 3.42*
	C. Iron	20	29.19±6.87	31.58±6.71*	20	31.57±4.36	34.42±4.62*	27	29.06±5.98	33.32±4.64*
MCV (fL)	Fe Asc	23	62.17 ± 6.42	75.82± 10.12*	22	62.20 ± 5.53	74.93± 10.35*†	35	62.54±6.73	79.53± 9.52*†
	C. Iron	19	70.05 ± 11.94	74.35 ± 11.50	19	69.59 ± 12.24	74.81 ± 7.86	26	66.01 ± 9.65	75.66 ± 11.48*
MCH (pg/cell)	Fe Asc	25	16.01± 3.04	22.99± 4.35*	24	15.61± 2.71	23.14± 3.92*†	37	16.25±3.17	24.83± 5.57*
	C. Iron	19	17.96 ± 5.17	21.69 ± 4.95*	19	18.24±4.40	21.33 ± 3.97*	26	16.70±4.24	22.44 ± 5.54*
MCHC (g/dL)	Fe Asc	25	25.69± 3.38	30.13± 2.60*	24	25.07± 2.30	30.75± 2.34*†	37	25.90±3.11	31.97± 1.97*
	C. Iron	19	25.28 ± 4.05	29.01 ± 4.19*	19	26.01 ± 2.42	28.39 ± 3.71*	26	25.06 ± 3.45	29.35 ± 4.10*
RC (%)	Fe Asc	23	1.36±1.67	0.81±0.91	23	1.09±1.50	0.56±0.48	35	1.17±1.51	0.73±0.55
	C. Iron	19	0.99±1.42	1.14±1.59	19	0.85±2.04	0.87±1.16	28	1.12±1.97	0.83±1.02

*All values are represented as Mean ±SD. * P Vs Baseline < 0.05; † P Value Between The Two Treatment groups <0.05; Fe Asc: Ferrous ascorbate; C. Iron: Colloidal iron; Hct: Hematocrit; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; MCHC: Mean Concentration Of Hemoglobin Per Volume of Red Cells; RC: Reticulocyte Count.*

Table 3. Change in Hb levels after 12 weeks of treatment

Group	Drug	n	Day 0	Week 12	
			Hb, gm% Mean ± SD (Range)	**Hb, gm%** Mean ± SD (Range)	**Responder Rate[#]** N (%)
All the children	Fe Asc	28	7.68 ± 1.5 (4.6 - 9.9)	10.91 ±1.63*† (7.8 - 13.5)	15 (53.57%) ‡
	C. Iron	29	8.18 ± 1.6 (3.7 - 10.0)	9.59 ± 1.55* (5.4 - 12.2)	3 (10.34%)
Severe anemia at Baseline	Fe Asc	8	5.74 ± 0.68 (4.6 - 6.9)	9.86 ± 1.64* (7.8 - 11.9)	3 (37.5%)
	C. Iron	8	6.08 ± 1.11 (3.7 - 6.9)	9.29 ± 2.21* (5.4 - 12.2)	1 (12.5%)
Moderate anemia at Baseline	Fe Asc	20	8.46 ± 0.90 (7.0 - 9.9)	11.34 ± 1.45*† (7.8 - 13.5)	12 (60.0%) ‡
	C. Iron	21	8.98 ± 0.85 (7.4 - 10.0)	9.71 ± 1.27* (6.9 -12.2)	2 (9.52%)

*Fe Asc: Ferrous ascorbate; C. Iron: Colloidal iron; # Responder rate defined as the proportion of children with Hb ≥11.5 gm% after 12 weeks of therapy. *P < 0.05 versus baseline (t test); † P < 0.05 between groups (t test); ‡ P < 0.05 between groups (Fisher's test).*

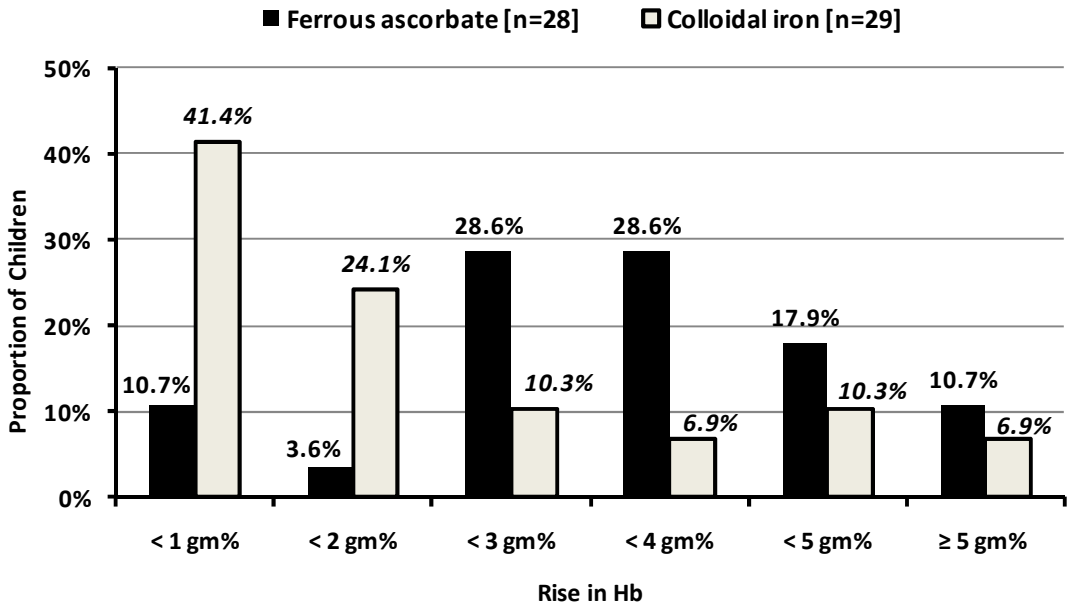

Figure 2. Frequency distribution of children in each treatment group based on the rise in Hb after 12 weeks of therapy

4. DISCUSSION

Ferrous ascorbate has been used as a reference iron formulation in many iron bioavailability and food fortification studies (Hallberg et al., 1984; Pizarro et al., 1998; Hallberg et al., 1986;

Bovell-Benjamin et al., 2000). Studies have demonstrated the efficacy of ferrous ascorbate in the treatment of IDA in adults (Agarwal et al., 2006; HERS Study Group India., 2005; Guinea et al., 1996).

The recommended dosage for iron supplementation ranges from 1 to 6 mg of elemental iron/kg/day based on the age and birth weight of the child (Choudhury et al., 2011; Stoltzfus et al., 1998; Guidelines and Protocols Advisory Committee, 2010). The dosage used in the present study was based on the recommendation by CDC (Centers for Disease Control and Prevention) and the Institute of Medicine which recommends treatment with oral iron at 3 mg/kg/d for 3 months (Bhargava et al., 2006).

The present study evaluates the therapeutic response of two marketed brands of iron syrup formulations in India. The purpose of choosing two marketed brands of iron syrup formulations was to understand and demonstrate the actual reflection of the drug's performance in practical settings. Colloidal iron syrup is very commonly used by pediatricians across India. Besides previous studies have focused on the comparison of ferrous ascorbate with other iron salts however, there is no data published so far which directly compares the efficacy of ferrous ascorbate and colloidal iron in children. Considering all these factors, colloidal iron was chosen as the comparator for this study.

This study demonstrates that ferrous ascorbate is an effective iron salt in the treatment of IDA in pediatric age group as well. The results of the present study show that ferrous ascorbate effectively increases the Hb level as compared to colloidal iron (mean rise in Hb 3.24 gm% versus 1.42 gm%) when given for a duration of 12 weeks. It is notable that the responder rate in children receiving ferrous ascorbate was significantly higher (53.57% versus 10.34% in colloidal iron group).

5. CONCLUSION

Favorable response and excellent acceptability with negligible side-effects shows that ferrous ascorbate is an effective iron salt in the management of IDA in children in comparison to colloidal iron, thus providing an evidence based choice for the appropriate iron preparation to be used in pediatric patients.

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COMPETING INTERESTS

Dr. Sutapa Ganguly, Dr. Tryambak Samanta, Dr. Dilip Kumar Paul and Dr. Radheshyam Purkait have no financial relationships with Zuventus Healthcare Ltd that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. Dr. Bhupesh Dewan and Ms. Nisha Philipose are employees of Zuventus Healthcare Ltd.

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