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Comparison of Ocular and Developmental Outcomes in Laser- and Bevacizumab-Treated Infants with Retinopathy of Prematurity

Short title: Outcomes in Treatment of Retinopathy of Prematurity

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Abstract

PURPOSE: To compare vision and developmental outcomes in infants who were treated with intravitreal Bevacizumab injection (IVB) versus laser for retinopathy of prematurity (ROP).

METHODS: Forty-two infants were enrolled in this study and treated with either IVB at 0.625 mg per eye, per dose (22 patients, 43 eyes), or laser (20 patients, 37 eyes) for type I ROP. Systemic complications were compared between these two groups. Structural examinations and cycloplegic refractions were performed at age 1 year. Body weight gains were collected from birth to 36 weeks of postnatal age. Neurodevelopmental assessment was done at 1 year chronological age.

RESULTS: At 1 year of age, four eyes (10.8%) in the laser-treated group and none (0.0%) in the IVB-treated group had unfavorable structural outcome; ten (30%) eyes in the IVB-treated group and 17 (53%) eyes in the laser-treated group were myopic, $p=0.03$; the mean spherical equivalent was -0.03 diopter (D) in the IVB-treated group and -2.94 D in the laser-treated group, $p=0.02$. The mean visual acuity in LogMar was 0.54 (SD, 0.34) and 0.58 (SD, 0.52) in the IVB- and laser-treated groups, respectively ($p=0.31$). The average weekly weight gain continued at normal rates in both groups after treatment. Seven of ten patients (70%) in the IVB-treated group and six of nine patients (67%) in the laser-treated group were categorized as severely developmentally delayed.

Conclusions: Bevacizumab intravitreal injection had similar short-term efficacy compared to laser treatment with regard to treatment of type I ROP but was associated with a lower prevalence of high myopia.

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness in the United States and worldwide.¹ Laser photocoagulation of the peripheral avascular retina is currently the standard treatment when type I ROP is diagnosed. Potential acute and long-term complications of laser treatment include pain, cataract, high myopia, and progression of the disease despite timely treatment. A treatment failure rate of approximately 9.1% has been reported with laser treatment, and additional treatment or surgery is sometimes required.² Recent reports have suggested that Bevacizumab has a beneficial effect on advanced ROP, and the agent is being used as monotherapy in several centers around the world.³⁻⁸ Data published from a multicenter clinical trial study showed that intravitreal Bevacizumab (IVB) monotherapy, as compared with conventional laser treatment, in infants with stage 3+ ROP showed a significant benefit for zone I but not for zone II disease.⁷ Immunohistology and pathology studies have demonstrated no obvious short-term toxicity to the retina, optic nerve, or other ocular tissues.⁴ The expression of vascular endothelial growth factor (VEGF) appeared not to be uniformly blocked in the developing tissues, allowing maturation of the mid-peripheral retina while restricting abnormal neovascularization.⁴ However, questions have arisen about Bevacizumab regarding short- and long-term safety to ocular tissues, other organs, and, especially, neurological development.^{6,9-11}

The purpose of this study was to compare ocular and developmental outcomes and systemic complications in infants who were treated with either IVB injection or laser for Type I ROP.

METHODS

Study Subjects

This is a cohort study to evaluate the efficacy and safety of IVB vs. laser for the treatment of type I ROP. The study was approved by the Institutional Review Board of Baylor College of Medicine/Texas Children's Hospital.

All infants with type I ROP who were treated with 0.625 mg IVB injection or laser from September 2010 to December 2012 were enrolled in this study. At the time of diagnosis of type I ROP, a full discussion of both treatment options was conducted with the parents in a manner intended to be completely unbiased. The advantages and disadvantages of each form of treatment were explained carefully, especially issues of the unknown possible late ocular and systemic side effects of IVB injection. The parents were provided with a written version of the issues discussed. The parents made the final decision regarding treatment. The following data were collected: gestational age (GA), birth weight (BW), primary diagnosis, duration of stay in the hospital, post-procedure pain management, systemic complications, vision outcomes, and development outcomes.

Diagnosis and treatment of type I ROP followed ET ROP guidelines.¹² Laser treatment was performed in the operating room under general anesthesia, and IVB injection was administered at the bedside under sterile conditions, using topical anesthesia and IV sedation with fentanyl if needed. Bevacizumab (Avastin®, Genentech Inc.) was injected into the vitreous of the affected eye (s) at 0.625 mg (in 0.025 mL solution) per eye, per dose. The injection procedure followed the protocol established by Mintz-Hittner (personal communication before the 2011 publication of the BEAT-ROP study results).⁷

Ocular Outcomes

Infants were followed closely after treatment to monitor resolution of the disease and to watch for the recurrence of vision-threatening ROP, until ROP was fully regressed and no abnormal vascular tissue was present that was capable of reactivation and progression.¹³ The definitions for treatment failure were: 1) recurrence of type I ROP or 2) stage 4A or higher retinal detachment. In both groups, if ROP recurred and met the treatment failure criteria, laser was used for type I or stage 4A ROP and intraocular surgery was used for stage 4B or higher retinal detachment. Structural outcomes of all eyes were documented with dilated fundus

examinations at 1 year chronological age. The definition of favorable vs. unfavorable structural outcome from the ET-ROP study was applied.² The best corrected visual acuity (VA) of each eye was measured at 2 years chronological age with Teller Acuity Cards. Unfavorable vision outcome was defined as best corrected VA of 20/200 or worse. Full cycloplegic refractive error was measured at 1 and 2 years chronological age. We used the standard definition of myopia and high myopia as in the ET-ROP study.¹⁴

Systemic and Developmental Outcomes

Systemic complications were documented and compared between the treatment groups. Short-term systemic events such as gastrointestinal bleeding, necrotizing enterocolitis, and hypertension (requiring treatment with anti-hypertensive medications) were documented. Body weight was documented weekly from birth to 36 weeks of postnatal age. Neurodevelopmental assessments were done between 6 to 12 months chronological age. Neurodevelopmental assessments were performed by board-certified, developmental-behavioral pediatric and neurodevelopmental disability pediatricians. Each neurodevelopmental assessment included a developmental history, direct behavioral observations, and direct developmental testing using the Revised Gesell Developmental Schedules; the Motor Quotient¹⁴ was used to assess gross motor development; and the Capute Scales,¹⁵ consisting of the Cognitive Adaptive Test and the Clinical Linguistic and Auditory Milestone Scale, was used to assess non-verbal, visual-motor problem-solving development and speech and language development. Developmental age equivalents derived from the developmental measures were converted to developmental quotient scores ($[(\text{developmental age} \div \text{chronologic age}) \times 100]$) for gross motor development, visualmotor problem-solving development, language development, and overall cognitive development. A developmental quotient score of 85 or more is considered normal; 71-84 is considered mild-to-moderate delay; and less than 70 is considered severe delay.^{28,16}

Statistical Analysis

Statistical analyses were performed using the IBM SPSS software version 20 (New York, USA). A *p*-value less than 0.05 was considered statistically significant. Demographic and clinical variables were summarized with descriptive statistics. Duration of stay was analyzed for inborn patients only. Two-tailed *t*-test was used for comparing group means. Chi-square and Fisher's exact test were used for proportions. Linear regression analysis was used to fit the growth model of body weight. The neurodevelopmental data were analyzed with student *t*-test matched paired and Wilcoxon signed-rank test with SPSS software.

RESULTS

Patient Characteristics

A total of 42 infants were included in our analysis: 22 patients (43 eyes) in the IVB-treated group and 20 patients (37 eyes) in the laser group. The clinical characteristics of the patients are listed in Table 1. Both groups were similar in baseline demographics in terms of APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores, incidence of co-morbidities, the mean gestational age and body weight at birth, and the mean postmenstrual age (PMA) and body weight at the time of treatment for type I ROP. Post-operative pain and sedation management was required for 3 of 22 (14%) patients in the IVB-treated group and 13 of 20 (65%) patients in laser-treated group ($p=0.009$). There was no significant difference in the length of hospital stay ($p=0.78$; Table 1).

TABLE 1. Comparison of Risk Factors and Other Characteristics of Patients with Type I Retinopathy of Prematurity in Bevacizumab and Laser Treated Groups

	IVB (n=22)	Laser (n=20)	<i>P</i> value
Birth weight, grams	645 ± 135	669 ± 145	0.59
Gestational age, weeks	24.3 ± 1.3	24.8 ± 1.8	0.46
Gender, male (%)	13 (59)	6 (30)	0.19
APGAR at 1 minute, median (range)	4 (1-8)	4 (2-8)	0.82
APGAR at 5 minutes, median (range)	7 (3-9)	7 (5-9)	0.80
Respiratory distress syndrome, n (%)	21 (95)	19 (95)	0.14
Bronchopulmonary dysplasia, n (%)	20(91)	16 (80)	0.47
Patent ductus arteriosus, n (%)	21 (95)	18 (90)	0.72
Culture-proven sepsis, n (%)	8 (36)	3 (15)	0.68
Intraventricular hemorrhage Grade 1 to 4, n (%)	16 (73)	13 (65)	0.94
PMA at treatment, weeks	35.7 ± 2.2	37.4 ±3.9	0.09
Body weight at treatment, grams	2046 ±485	2347 ± 940	0.19
Post-operative pain and sedation management, n (%)	3 (14)	13 (65)	0.009
Duration of hospitalization, days	153± 52	158± 58	0.78

IVB = Intravitreal Bevacizumab; APGAR=an acronym for Appearance, Pulse, Grimace, Activity, and Respiration; PMA = postmenstrual age (gestational age + weeks since birth).

The severity of ROP in the affected eyes at the time of treatment was similar in these two groups (Table 2). There were no intraocular infections in either group. Laser treatment (and lid speculum time) for ROP took 20-30 minutes per eye, and IVB injection required use of a lid speculum for 1-2 minutes. We did not routinely check intraocular pressure (IOP) with equipment unless there was reason to suspect an increase in IOP by tactile palpation or cloudy cornea. By assessment of tactile tension and corneal clarity, none of the patients in this study developed increased IOP after undergoing the procedure.

TABLE 2. Comparison of Status of Type I Retinopathy of Prematurity at the Time of Treatment

	IVB (n=22)	Laser (n=20)	<i>P</i> value
Right eye only, n (%)	1 (5)	2 (10)	0.53
Left eye only, n of patients (%)	0 (0)	1(5)	0.29
Both eyes, n of patients (%)	21 (95)	17 (85)	0.28
Right eye, n of patients (%)			
Zone 1	3 (14)	1 (5)	0.33
Zone 2	19 (86)	16 (84)	0.86
Zone 3	0 (0)	2 (11)	0.12
Plus disease	21 (95)	19 (100)	0.34
Stage 2	6 (27)	4 (21)	0.65
Stage 3	16 (73)	15 (79)	0.43
Left eye, n of patients (%)			
Zone 1	4 (19)	3 (17)	0.49
Zone 2	17 (81)	15 (83)	0.87
Zone 3	0 (0)	0 (0)	
Plus disease	21 (100)	18 (100)	0.34
Stage 2	10 (48)	10 (56)	0.61
Stage 3	11 (52)	8 (44)	0.64
IVB = Intravitreal Bevacizumab			

IVB-treated Eyes

In the IVB-treated group, there were seven eyes (3 right eyes; 4 left eyes) with zone I disease and 36 eyes (19 right eyes; 17 left eyes) with zone II disease (Table 2). All zone I ROP regressed fully after one injection. Of the 36 eyes with zone II disease, three eyes (8.3%) underwent laser treatment for recurrence of type I ROP. One patient was born at 24 weeks GA and treated with IVB initially for zone II/stage 2+ ROP in both eyes. The plus disease disappeared within 3 days after the injection and ROP regressed two weeks after the injection. However, type I ROP recurred bilaterally 84 days after the initial injection and was rescued with **lasertreatment**. Another patient was born at 22 weeks GA and was initially treated with IVB for zone II/stage 3+ ROP in both eyes. The plus disease got better 2 days after injection and ROP started regressing in both eyes initially. However, the regression stopped in the right eye 13 days later and type I ROP recurred 18 days after the injection. This eye was rescued by laser. All ROP in the IVB-treated group eventually regressed fully. No patient in the IVB-treated group developed a retinal fold involving the macula.

Laser-treated Eyes

In the laser-treated group, there were four eyes (1 right eye; 3 left eyes) with zone I disease, 31 eyes (16 right eyes; 15 left eyes) with zone II and 2 eyes (right eye) with zone III disease (Table 2). Two of the four eyes (from one patient, 50%) with zone I disease required surgery for development of stage 5 ROP, 53 days after the initial laser treatment. Two of the 31 eyes (6.5%) with zone II (zone II) disease required surgery for stage 5 ROP 44 days after receiving the initial laser treatment. Of these re-treated patients, one was born at 23 weeks GA (inborn, zone I/stage 2+) and the other one was born at 24 weeks GA (transferred from the other hospitals for the treatment of ROP, posterior zone II/stage 3+).

At 1 year of age, no eyes in the IVB-treated group and four eyes (zone I=2; zone II=2; 10.8% total) in the laser-treated group had unfavorable structural outcomes according to the ET-ROP definition (Table 3).

TABLE 3. Structural Outcomes at Ages 1 and 2 Years for Bevacizumab- and Laser-Treated Infants with Type I Retinopathy of Prematurity

ROP	Retreated eyes N (%)		P value	Unfavorable structural outcomes at age 1 year ^a N (%)		P value
	IVB (n=43 eyes)	Laser (n=37 eyes)		IVB (n=43 eyes)	Laser (n=37 eyes)	
Zone 1 ROP	0 (0)	2 (50)	0.0001	0 (0)	2 (50)	0.0001
Zone 2 ROP	3 (8.3)	2 (6.5)	0.83	0 (0)	2 (6.5)	0.04
Zone 3 ROP	-	0 (0)	N/A	-	0 (0)	N/A
Total	3 (7.0)	4 (10.8)	0.33	0 (0)	4 (10.8)	0.02

IVB = Intravitreal Bevacizumab; ^a The unfavorable structural outcomes at age 2 years remained same as age 1.

Primary Outcomes

At age 1 year, in IVB-treated group, two patients died and three patients lost follow-ups. One IVB patient died from an acute cardiopulmonary arrest and suspected myocardial infarction 142 days after the injection. The other IVB patient died from multi-system complications 151 days after the injection. In laser-treated group, two patients died and two patients lost follow-ups. One laser patient died 92 days after laser treatment from multi-system failure with concomitant patchy pulmonary interstitial glycogenesis. The other laser treated patient died 180 days after laser as a result of an acute decompensation with bradycardia and desaturations. Thirty-three eyes in IVB-treated group and 31 eyes in laser-treated group had cycloplegic retinoscopy examination at 1 and 2 years chronological age; the refractive error (RE) results are shown in table 4. In laser-treated group, one patient developed unilateral secondary cataract and had

cataract surgery. This aphakic eye (RE +16.00) was eliminated from the statistical analysis. At age 1 year, the eyes treated with laser were significantly more myopic than were those treated with IVB ($p=0.03$) (Table 4). The proportion of patients who had high myopia was significantly higher in laser-treated group. At the age of 2 years, both groups showed progression of myopia, but the laser-treated group experienced more progression of myopia than did the IVB group. The distributions of the spherical equivalent (SE) at 1 and 2 years are shown in table 4.

TABLE 4. Percentage of Eyes with Myopia and High Myopia in the Bevacizumab and Laser Treated Groups at age 1 and 2 Years

Refractive status	IVB	Laser	<i>P</i> value
Eyes with any myopia ≥ 0.25 D, n/N (%)			
1 year	10/33 (30)	17/31 (55)	0.03
2 years	16/28 (57)	20/25 (80)	0.002
Eyes with high myopia ≥ 5 D, n/N (%)			
1 year	3/33 (9)	10/31 (32)	0.006
2 years	3/28 (11)	14/25 (56)	0.0005
Refractive errors, SE Mean ± SD (range)			
1 year	-0.03 ± 2.91 (-7.00 to +4.00)	-2.94 ± 4.42 (-12.0 to +5.00)	0.02
2 years	-1.22 ± 2.95 (-7.50 to 4.00)	-5.61 ± 4.50 (-16 to 1.0)	0.03
IVB: intravitreal Bevacizumab; SE: spherical equivalent; D = diopter; SD = standard deviation; n= number of eyes with myopia; N=total number of eyes examined.			

Vision testing with Teller acuity cards was performed on 28 eyes in the IVB-treated group and 25 eyes in the laser-treated group at age 2 years. Two eyes (7%) in the IVB-treated group and four eyes (16%) in the laser-treated group had the best corrected VA below 20/200, $p=0.21$. In the IVB-treated group, one child (2 eyes) had an unfavorable visual outcome: light perception

vision due to severe periventricular leukomalacia (PVL) and optic pathway hypoplasia. For this child, the ROP was fully regressed and no retinal structural abnormality was seen at age 2 years. The mean VA in LogMar was 0.54 (SD, 0.34) and 0.58 (SD, 0.52) in the IVB- and laser-treated groups, respectively ($p=0.31$).

Growth Curve

Body weight was measured weekly, from birth to 36 weeks postnatal age. The growth curve for each group was plotted with mean body weight of the same postnatal age. The growth curves were obtained for pre- and post-treatment. The body weight showed linear increase with age in all groups. The correlation coefficient (r^2) between the average body weight and postnatal age was 0.97 ($p=0.005$, pre-treatment) and 0.98 ($p=0.001$, post-treatment) in the IVB-treated group, and was 0.93 ($p=0.05$, pre-treatment) and 0.92 ($p=0.007$, post-treatment) in the laser-treated group. The two groups had similar growth curves for both before and after treatment. The average weight gain before ROP treatment was 126.9g/week (SE, 7.7) in the IVB-treated group and 128.1 g/week (SE, 6.1) in the laser-treated group, $p=0.16$. After receiving treatment for ROP, the average weight gain was 137.4g/week (SE, 3.0) in the IVB-treated group and 143.1g/week (SE, 4.6) in the laser-treated group, $p=0.10$. Faster weight gain occurred after treatment in both groups compared to pre-treatment, $p=0.007$ in the IVB-treated group and $p=0.003$ in the laser-treated group.

Neurodevelopmental Assessments

Ten patients from the IVB-treated group and nine patients from the laser-treated group underwent neurodevelopmental assessments at 6 to 12 months chronological age. Table 5 shows the history of seizures, GA and mean developmental quotient scores in the IVB- and laser-treated groups. The ranges of developmental quotient scores in all tested subgroups were broad, ranging from 17 to 84 in the IVB-treated group and from 20 to 80 in the laser-treated group. Seven of ten patients (70%) in the IVB-treated group and six of nine patients (67%) in the

laser-treated group were categorized as severely developmentally delayed (developmental quotient score less than 70) according to the gross motor developmental quotient scores.

TABLE 5. Developmental Assessment for Infants Treated with Bevacizumab and Laser for Type I Retinopathy of Prematurity

	IVB N=10	Laser N=9	<i>P</i>
Gestational age	24.6 ±1.2	24.0 ± 0.0	0.67
IVH grade 3-4, n (%)	5 (50%)	4 (44%)	0.79
Hydrocephalus with VP shunt, n (%)	4 (40%)	2 (22%)	0.41
History of seizure, n (%)	1 (10%)	1 (11%)	0.94
Developmental quotient scores			
Gross motor	55.7 ± 25.9	53.2 ± 21.2	0.78
Visual motor	49.4 ± 20.5	51.4 ± 23.3	0.84
Language	47.8 ± 19.8	50.4 ± 20.8	0.84
Cognitive	48.6 ± 19.6	50.9 ± 21.7	0.83
IVB= intravitreal Bevacizumab; IVH = Intraventricular hemorrhage; VP = Ventriculoperitoneal			

DISCUSSION

Several multicenter clinical trials have analyzed the efficacy of different interventions proposed to minimize the negative visual outcomes associated with ROP.^{7, 17,18,19,20} VEGF is an important component of the pathogenesis of ROP. Anti-VEGF therapy by IVB emerged as a potential therapy in 2007.^{3,7} However, studies showed that Bevacizumab leaks into the blood stream and reduces the serum level of VEGF,²¹ which could potentially cause systemic complications with a negative impact on neurodevelopment. In this study, we found no post-

treatment hypertension or exacerbation of NEC in either group. In both groups, the mortality rates were lower than the national rates reported for premature infants with BWs less than 1500g in the 2007 linked file: 17.8% for GA <32 weeks and 24.5% for BW <1500 grams.²²

In this study, we used body weight gain as one of the development parameters to assess the effect of systemically absorbed Bevacizumab on general growth. The typical pattern of weight changes in infants is a variable degree of initial weight loss, followed by limited weight gain (70–150 g) between 10 and 20 days. Growth velocity, the change in growth over time, is a more sensitive index of growth than is a single measurement. Normal full-term infants lose 10% of body weight in the first 2 weeks after birth; they then gain an average of 30 grams (1% of body weight) per day until they reach 3 months of age, and then 20 grams per day until they are 6 month of age.²³⁻²⁵ In low-birth-weight preterm infants, an absolute growth rate is a reliable indicator of the weight growth pattern during the first year of life, and there is no significant difference in gender.²⁶ Studies have shown that preterm infants who were born at less than 30 weeks postmenstrual age with BW less than 1250 grams have an average weight gain of 16 grams per day.²⁶ In our study, the absolute weight gains in both groups before treatment were similar and consistent with the published data.²⁶ After treatment, significantly faster weight gain occurred in both groups, compared to pre-treatment, $p=0.007$ in the IVB-treated group and $p=0.003$ in the laser-treated group. There was no significant difference of the rate of body weight gain between the two groups, $p=0.1$. Our hypothesis is that the faster weight gain experienced after receiving the IVB injection and laser treatment was possibly due to up-regulation of insulin like growth factor (IGF-1).

This study didn't detect differences in developmental quotient scores. The Gessell Developmental Schedule is used by pediatricians to identify infants at risk for neurological impairment and mental development delay. An uncorrected developmental quotient score is suggested to be a more sensitive index for identifying abnormalities in preterm infants.^{27,28} A

low developmental quotient score is often related to intraventricular hemorrhage with or without ventricular dilation.^{28,29} Although early developmental tests have limited ability to predict future Intelligence Quotient (IQ), their predictive power is better for children with significant developmental delays. Tests of early child development, such as the Capute Scales and Bayley Scales, were designed to separate normal from abnormal, not to separate subtle degrees of normality. However, infants and children without disabilities have greater variability and less stability of developmental scores over time than do children with cognitive disabilities. In this study, half of the infants had developmental assessment at between 6 to 12 months of chronological age. We are not able to draw any meaningful conclusion due to the small sample size and the broad range of developmental quotient in each group. However, these data could provide important information for the planning and justification of a randomized controlled multicenter trial in the future.

Laser surgery has been confirmed as a safe and effective treatment for ROP.^{12,30} The postoperative inflammation and the need for post-operative analgesics is significantly less compared to cryotherapy.³¹ The results from this study showed that the need for post-treatment pain management in the IVB-treated group was significantly less than in the laser-treated group. Previous reports indicate that although VEGF inhibition for treatment of ROP is promising and can allow further retinal vascularization, late recurrences of ROP are possible.^{32,33} In this study, 3 of 43 eyes (6.9%) in the IVB-treated group needed laser rescue after one IVB injection. In one patient, type I ROP recurred 84 days after the initial injection, suggesting that long-term postoperative follow-ups should be considered in certain IVB-treated patients.

For the majority of the patients, and all with zone I disease, type I ROP resolved fully after one IVB injection. Although 3 (7.0%) patients in the IVB-treated group required laser rescue, ROP resolved eventually without unfavorable structural changes. The unfavorable

structural outcome in our laser-treated group is 10.8%; in the ET-ROP study, 14% of patients with type I ROP showed unfavorable structural outcome at age 9 month.

Our study applied the same injection dose as in the BEAT-ROP study. Reducing the Bevacizumab dose could decrease the potential risk for systemic complications. Future studies are necessary to address these questions: 1) Is the commonly used dose (0.625mg per eye per injection) the proper one? and 2) How can we optimally select the ideal dose for the individual patient? Serum VEGF levels or serum levels of other growth factors may provide useful information, potentially leading to individualized treatment.

Conclusion

Our pilot study showed that IVB is comparable to laser therapy for treatment of type I ROP, especially for zone I disease. IVB had a more favorable side effect profile than did laser therapy, and that the prevalence rates of high myopia were lower in the IVB-treated group, compared with the laser-treated group. The potential for delayed complications from anti-VEGF therapy remains a major concern. A large, randomized, controlled trial is necessary to answer these concerns.

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