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Scientific Review

Propranolol for Infantile Hemangiomas: Early Experience at a Tertiary Vascular Anomalies Center

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Objectives/Hypothesis: Propranolol has recently been introduced as a novel pharmacologic treatment for infantile hemangiomas. Systematic examination of this treatment in a tertiary care setting has not been described. This study explores the impact of propranolol on both proliferative and involuting hemangiomas at a tertiary vascular anomalies center.

Study Design: Retrospective single institution review.

Materials and Methods: We reviewed children treated with propranolol for problematic hemangiomas followed by a blinded prospective analysis of serial photographs taken during the course of their therapy. Parental questionnaires were obtained to evaluate perceived therapeutic response and complications to oral propranolol.

Results: Thirty-two children with complete photo documentation were treated with oral propranolol for infantile hemangiomas between September 2008 and June 2009. Twenty-seven patients began therapy during the proliferative phase of their lesions (mean age, 4.9 months), whereas five patients began during the involutional phase (mean age, 19.4 months). Ninety-seven percent of patients displayed improvement in the quality of their hemangiomas during propranolol therapy. Patients were determined to be excellent responders (n = 16, 50%), partial responders (n = 15, 47%), or nonresponders (n = 1, 3%). Partial and nonresponders received adjuvant therapy (75%, laser therapy; 31%, steroid injections). Ten patients experienced minor but reportable side effects to propranolol, including somnolence (27.2%), gastroesophageal reflux (9.1%), respiratory syncytial virus exacerbation (4.5%), and rash (4.5%).

Conclusions: Propranolol may revolutionize the treatment of problematic hemangiomas that cause imminent functional or cosmetic sequelae. At therapeutic doses, propranolol is safe and effective in the majority of patients. Adjunctive therapies may still be required. Minor side effects, expected from beta-blocker therapy, are common but easily managed.

Key Words: Propranolol, hemangioma, birthmark, beta-blocker.

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INTRODUCTION

Infantile hemangiomas comprise the majority of vascular anomalies and are considered the predominant vascular tumor type. Hemangiomas affect nearly 4% to 10% of infants and have been found to have unique, but natural phases of proliferation (growth) and involution (dissolution).[1–4] If present in inconspicuous sites, hemangiomas are frequently left untreated and allowed to follow their natural course. However, problematic hemangiomas occur when they ulcerate, have massive growth, cause disfigurement, or impact normal function or cosmetic development.[2,5] Common locations for problematic hemangiomas include the face, ear, orbit, and airway. These hemangiomas subsequently require early and aggressive treatment for ideal functional and cosmetic outcomes.[5]

Current treatment options for problematic hemangiomas include systemic or intralesional corticosteroids, chemotherapeutic agents (vincristine, alpha-interferon), laser, surgery, or a combination of these therapies.[6–8] Unfortunately, each treatment option has limited therapeutic benefit with its own side-effect profile and risks.

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Recently, Leaute-Labreze and colleagues reported the serendipitous finding that hemangiomas regress in newborns treated with propranolol, a known nonselective beta-blocker used in treating infants with cardiac and pulmonary conditions.[9] This finding has been supported by a few additional case reports.[10–13] Systematic examination of the use of propranolol in a tertiary care setting has not yet been described. Similarly, the side effect profile of propranolol in children is still not well documented. In this study, we explore the impact of propranolol on both proliferative and involuting hemangiomas at our vascular anomalies center. Using parental questionnaires and blinded observers we document the perceived response of propranolol therapy on these lesions.

MATERIALS AND METHODS

Approval for this study was obtained by the institutional review board of the University of Arkansas for Medical Sciences. Patient charts were reviewed for those treated with propranolol for problematic hemangiomas from September 2008 through June 2009. Problematic hemangiomas were defined as hemangiomas with imminent undesirable functional or cosmetic outcomes if left untreated. Alternative interventions (steroid injections, laser, and surgery) would have been performed in these patients despite the availability of oral propranolol. Consent to treat with propranolol and document disease response was received from all parents with infants and children participating in this study.

Treatment Protocol

As previously described by our vascular anomalies center,[10] a protocol for use of propranolol in children with problematic hemangiomas was determined by the center in collaboration with pediatric cardiology team at Arkansas Children's Hospital. An oral dose of 2 mg/kg/day divided three times daily (TID) was deemed safe and potentially effective as determined by Leaute-Labreze and colleagues.[9] In brief, a careful patient history and physical is performed to ascertain risk factors or contraindications to using propranolol. Specific questions pertaining to reactive airway disease, asthma, lung or heart problems, hypoglycemia, and reflux are asked. If present, additional work-up is performed or the patient is not offered propranolol therapy. Baseline electrocardiograms (ECG) are conducted and interpreted by a pediatric cardiologist for all treatment candidates. Prior cardiac history, suspected heart blocks, or other abnormal findings on ECG warrant an echocardiogram prior to therapy initiation. Patients with a history of prematurity, lung, or cardiac conditions are admitted for overnight monitoring at the onset of propranolol treatment (n = 2 in this study). Infants and children cleared for propranolol use began at home at a dose of 2 mg/kg/day divided TID. Dose adjustments (to weight) and patient assessments by telephone interaction or clinic visits were performed monthly. In patients with proliferating lesions, treatment proceeded from the proliferative phase to the theoretic conclusion of hemangioma growth at 12 months of age. One initial patient with an excellent early response was weaned off propranolol at 5 months of age, only to have rebound growth after cessation. Thus, our protocol has been to continue therapy until 12 months of age. Patients in the involutional phase remained on propranolol for at least 6 months and until resolution or observation of benefit ceases. Propranolol is weaned at the end of treatment, as recommended by our cardiology team for most beta-blockers, by reducing the dose by one half for 1 to 2 weeks, then stopping. Partial and nonresponders to propranolol underwent adjuvant therapy that included one or more of the following approaches: flash pulse-dye laser, steroid injection, or surgical excision.

Photograph Analysis

After receiving consent, photographic documentation of all lesions is performed on all patients presenting to our vascular anomalies center. Hemangiomas undergoing propranolol therapy were photographed in series before and during their treatment cycle. Interval exams with photographs were performed to document treatment response. Formal review of the photographs was performed by five blinded observers who were physicians with variable levels of experience in the treatment of vascular anomalies. Disease response was graded for each patient from onset of therapy to final photo documentation. Hemangiomas were numerically rated with 0 = growth of hemangioma, 1 = stable (no growth or improvement), 2 = some improvement, 3 = significant improvement, and 4 = resolution.

Parent Questionnaire

A questionnaire was developed by the vascular anomalies center to assess the impact of propranolol treatment from the perspective of close observers (parents) of the patients over their treatment course. Families were included if their child had received propranolol for the treatment of a problematic hemangioma for a period of 1 month or greater. The questionnaire included the following questions designed to be in terms that are easily interpreted by a nonmedical layman:

- How long before you noticed a difference in your child's hemangioma?
- Have you noticed a color change in the skin?
- Have you noticed less protrusion or shrinking of the portions that stick out?
- Did your child have any unusual behaviors or side effects from the medication?
- Describe your overall opinion of propranolol.

The answers were recorded via phone interview prospectively.

RESULTS

Over a 10-month period, 41 patients with infantile hemangiomas were started on oral propranolol. Thirty-two patients had sufficient data and photo documentation for complete review (27 = female, 5 = male, 5.1:1 ratio). Mean age at therapeutic initiation was 7.1 months (range,1.5–30 months). Patients in the both the proliferative (n = 27) and involuting (n = 5) stages of hemangioma growth were treated at a mean age of 4.9 and 19.4 months, respectively. Hemangioma locations included the nasal tip (n = 9), periorbital (n = 8), cheek (n = 5), trunk (n = 4), parotid gland (n = 3), neck (n = 3), subglottis (n = 3), extremity (n = 3), glabella (n = 2), lip (n = 2), and ear (n = 2) (Fig. 1). Several patients had overlapping hemangiomas involving more than one anatomic site.

Prior to propranolol therapy, 15 patients (47%) suffered a complication related to hemangioma growth including ulceration (n = 7, 21.9%) (Fig. 1), ptosis and/or visual field obstruction (n = 5 patients, 15.6%), bleeding (n = 2, 6.25%), and airway obstruction (n = 2, 6.25%). One patient suffered two complications. Twenty-one of

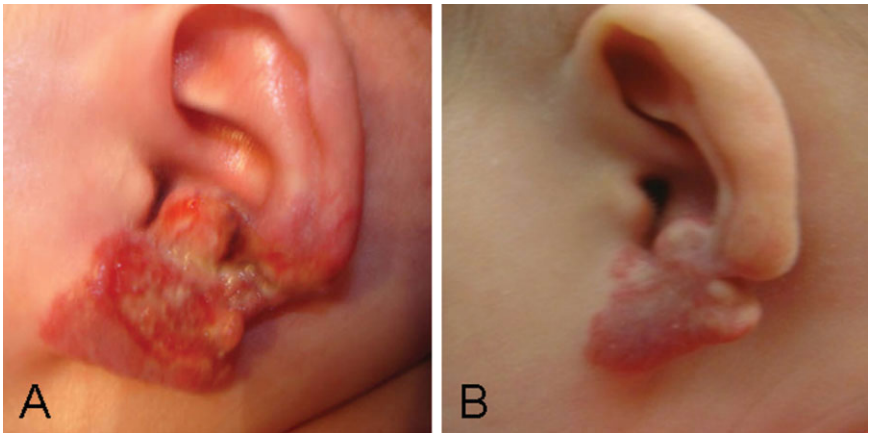

Fig. 1. (A) Patient before initiation of treatment. (B) Patient after 2 months on propranolol alone.

the 27 patients (77.8%) with proliferating hemangiomas received no prior treatment to propranolol. In contrast, four of the five patients with hemangiomas in the involutional stage had been treated with either oral or injected steroids, carbon dioxide (CO_2) and/or pulse dye laser, or systemic chemotherapy (vincristine). As awareness increased regarding propranolol as a therapeutic option, these patients were started when complete response to alternate therapies was not evident (mean follow-up, 5.5 months; range, 2–10 months). Four patients, at the writing of this paper, have been weaned off the propranolol at 11 to 12 months of age with no evidence of rebound or recurrence.

Serial patient history, physical exam, and photo documents were reviewed by the first author to assess response to oral propranolol therapy. Nearly every patient (97%, n = 31) treated with propranolol displayed some improvement of their lesions. Specifically, 16 of the 32 patients reviewed (50%) required no additional therapy (mean follow-up, 5.5 months) and were deemed excellent responders to propranolol and requiring no additional therapy (Fig. 1). Fifteen patients (46.9%) demonstrated improvement in growth and size of their hemangiomas but underwent adjuvant therapy to compliment their treatment before or after the initiation of propranolol (Fig. 2 and Fig. 3). These patients were considered to be partial responders. Only one patient (3.1%) had persistent hemangioma growth despite propranolol therapy and was termed a nonresponder requiring alternate therapy (Fig. 4). Four patients had complete resolution with no residual evidence of disease (Fig. 2 and Fig. 3).

Adjuvant therapies used in this study included flash pulsed dye laser (FPDL) (n = 12, 75%) (Fig. 2), steroid injection (n = 5, 31.2%) (Fig. 3), and surgical excision (n = 3, 18.8%). FPDL was performed in patients with frank or impending ulceration, and steroid injections were performed in patients with periorbital lesions causing functional impairment. Surgery was performed on the one nonresponder for a large periorbital lesion (Fig. 4) and in two others for residual fibrofatty tissue. The five patients in the involutional stage of the hemangioma cycle had undergone a mean of 4.2 other treatments prior to beginning propranolol (e.g., FPDL, CO_2 laser, oral/injected steroids, partial excisions, and vincristine). After treatment initiation, four of the five patients required no further treatment, and one patient underwent a single FPDL treatment to date.

Photograph Analysis

Serial photographs of patients were taken during the course of their problematic hemangioma treatment with oral propranolol. Five blinded physicians both experienced (n = 1) and inexperienced (n = 4) with vascular

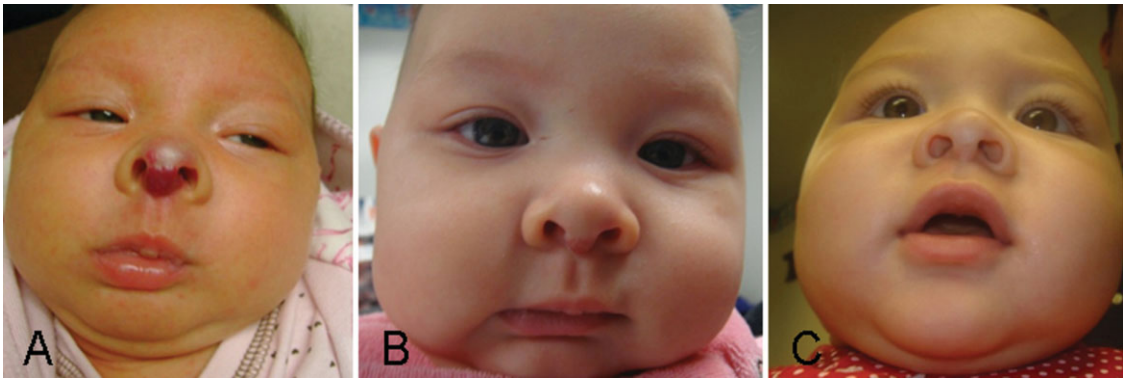

Fig. 2. Patient who received propranolol and pulsed dye laser treatments every 3 months. (A) Pretreatment. (B) Two months on propranolol with one laser treatment. (C) Six months on propranolol with three laser treatments.

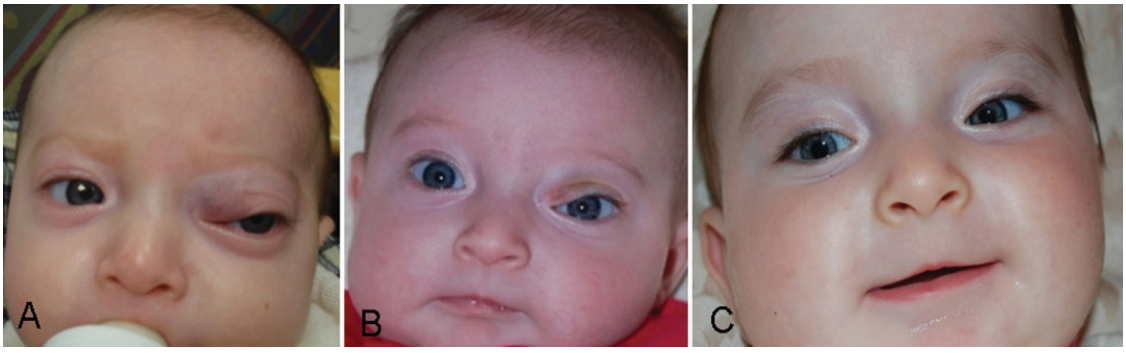

Fig. 3. Patient who received propranolol and one intralesional steroid injection into a large orbital hemangioma. (A) Pretreatment. (B) One month on propranolol. (C) Six months on propranolol.

anomalies were asked to review the photographs for this study. Response scores indicated that hemangiomas changed in size and appearance toward resolution throughout the course of their propranolol therapy (Fig. 5). Average response scores were 2.38, 2.40, 2.69, and 3.51 after 1 month, 2 months, 3 to 4 months, and >5 months of propranolol therapy, respectively. Similar to clinical findings, four patients were considered to have complete resolution by their response raters (mean follow-up, 5.5 months).

Parent Questionnaire

Twenty-two patients treated with propranolol for >1 month were provided parental questionnaires regarding the therapeutic response. All parents subjectively noticed a difference in their child's hemangioma. The time for this to occur was on average <1 week from the onset of therapy in eight patients (36%), <1 month in 10 patients (45.4%), and 1 to 2 months in four patients (18.2%). Therapeutic responses were clarified regarding the deep and superficial components of the hemangiomas. All parents (100%) noticed improvement in the deep components of the hemangioma; 17 (77%) noted improvement in the superficial portions of the hemangioma. Their overall opinion of propranolol treatment was "happy with the response, would recommend" in 20 of 22 patients (90.9%) and "neutral" in 2 of 22 patients (9.1%). The two neutral responses included one child who had continued growth while on propranolol (Fig. 5) and another who developed a psoriatic-like rash that required cessation of treatment.

Reported Side Effects

Propranolol was suspected to be the cause of side effects reported by 10 of 22 families inquired (Table I). Minor side effects included increased somnolence (n = 6), gastroesophageal reflux (n = 2), allergic rash (n = 1), and respiratory syncytial virus exacerbation (n = 1). There were no reports of serious side effects related to cardiac events, bronchospasm, or hypoglycemia. Nearly every patient with reported side effects was managed with propranolol dosing adjustments to <2 mg/kg/day. One patient required cessation of therapy due to psoriatic-like rash.

DISCUSSION

Hemangiomas are the most common benign tumor in infancy.[4,14] Although the majority have little impact on childhood health, various problematic head and neck hemangiomas will develop rapidly and interfere with normal function and appearance. These problematic hemangiomas require intervention to control growth

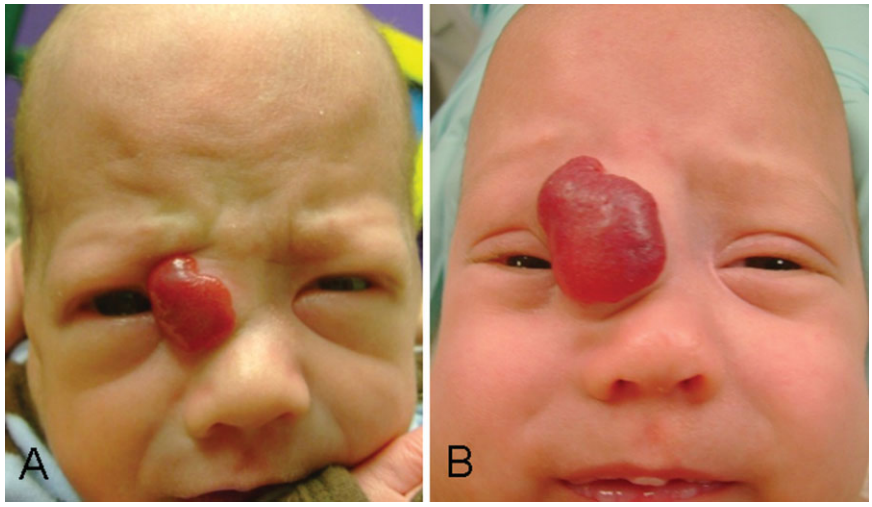

Fig. 4. Patient who had no response to propranolol or steroid injection. (A) Pretreatment. (B) Two months on propranolol and one steroid injection.

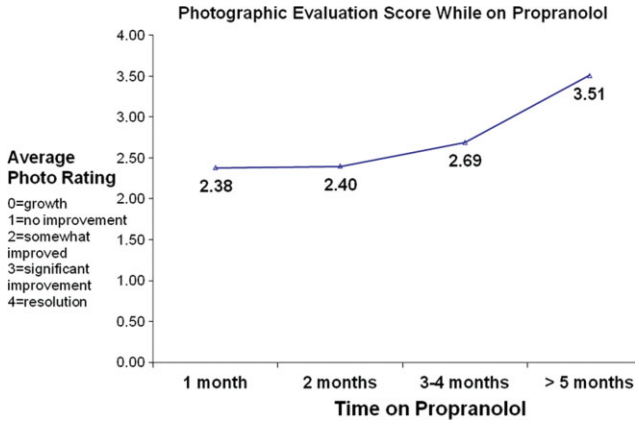

Fig. 5. The average photo rating of five blinded reviewers over a period of time while treated with propranolol. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and reduce the likelihood of imminent functional and cosmetic deformities.[5] Propranolol was recently found to lighten and reduce the size of hemangiomas during the proliferative phase of development.[9] The mechanism of action and pathophysiology behind this discovery remains unclear. Theories suggesting that propranolol impacts hemangioma growth through the induction of apoptosis and antiangiogenic activity are gaining support. Nevertheless, several case studies have further provided evidence of the dramatic effect of propranolol on massive, proliferating, life threatening, and involuting lesions.[10,11,13]

Since the introduction of propranolol as a treatment option for problematic hemangiomas, our vascular anomalies center offered this therapy for off-label use to help manage over 40 children with these lesions in various stages of growth. As evident by this report, the vast majority (over 95%) of lesions respond to oral propranolol at 2 mg/kg/day with few or limited side effects. Because some of the more problematic lesions (periorbital, airway, ulcerations) required urgent therapy, time tested adjuvant therapies were used to prevent untoward functional deficits as propranolol therapy was initiated. Regardless, a range of propranolol's effectiveness is apparent with nearly 50% of children requiring alternate treatment to improve disease resolution. Only four patients had complete eradication without visible evidence of disease on propranolol (one patient received propranolol alone, two patients had one steroid injection each, and one received laser treatment). The reason for the one nonresponder remains enigmatic.

Although not explicit in this report, anecdotal evidence by the practitioners and parents involved in this study suggest that most of the improvement occurs within the deep components of the hemangioma. Superficial disease with bright red involvement of the dermis and epidermis was often less responsive and required laser therapy to improve cosmesis. In the authors' experience, control of the deep elements is more critical to functional and cosmetic sequelae, as this reduces the need of surgical intervention and further validates the role of propranolol in the treatment of hemangiomas. This has been particularly true for two patients with airway disease. Similarly, both parents and practitioners in this study recognized disease improvement near 2 to 4 weeks from the onset of therapy. Four patients have so far been weaned from propranolol with no evidence of rebound or recurrence. Long-term follow-up remains paramount for understanding and accepting propranolol as a potential first-line treatment for hemangiomas.

These findings stimulate questions regarding the possible mechanisms of action of propranolol on vascular tumors. Variability in response also suggests the possibility of variability in tumor composition in hemangiomas. Basic science examination of the pharmacologic mechanism of propranolol is underway. We suspect that induction of apoptosis is the primary effect of propranolol on hemangiomas as recently identified in pancreatic cancer cells.[15]

Due to the limited literature and research available on the impact of propranolol on hemangiomas and other vascular tumors, a precise protocol for its clinical use does not yet exist. Our vascular anomalies center initiated, following discussion and collaboration with pediatric cardiology, a standard approach to the use of low-dose propranolol in our patient population with problematic hemangiomas. As previously reported,[10] specific guidelines regarding the appropriate patients, follow-up, and dosing adjustments have been established to reduce untoward cardiopulmonary or systemic effects of this medication. Current dosing of 2 mg/kg/day was considered, by our cardiology team, to be below the therapeutic range for other vascular or cardiac conditions and subsequently maintained little risk to our otherwise healthy patients. This study is limited in that our treatment protocol does not address dose-related responses for alternate dosing regimens. Similarly, a direct comparison to other treatment modalities has not been performed. Nonetheless, this preliminary report supports the use of propranolol in problematic hemangiomas as an alternate or complimentary treatment tool that is effective in proliferative, involuting, and otherwise treatment recalcitrant lesions. Response to higher doses may be more dramatic as seen in one patient who unintentionally (pharmacy error) received 4 mg/kg/day for 1 month and had complete resolution of disease. This needs to be balanced with potential increased risk of side effects to beta-blocker therapy. Prospective trials are currently being performed at several treatment centers around the world, which will better answer these questions.

TABLE I.
Side-Effect Profile of 22 Patients on Oral Propranolol for Treatment of Problematic Hemangiomas.

Side Effect	No. Patients (%)
Increased sleepiness	6 (27.3)
Gastroesophageal reflux	2 (9.1)
Allergic rash	1 (4.5)
Respiratory syncytial virus exacerbation	1 (4.5)

Side effects, although not uncommon, tended to be minor with the most frequently reported being somnolence and reflux. The somnolence tended to last for 3 to 7 days after dosage increases and then typically subsided. Antireflux medications were added in symptomatic patients. The psoriatic-like rash is a rare side effect, which can be seen with beta-blockers. In this patient, extensive use of topical steroid creams made continuation of the propranolol impossible. Overall, all side effects reported in our patients were considered minor. Careful screening for asthma, hypoglycemia, and other cardiac problems was instrumental in keeping more life-threatening side effects from occurring.[12]

CONCLUSION

Propranolol appears to be a valuable and effective treatment option for infantile hemangiomas. It has a tolerable side-effect profile, and there have been no serious side effects reported in appropriately screened patients. Propranolol is likely to revolutionize the management of hemangiomas and may offer the best medical treatment to date for this purpose.

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