Assessing the Impact of Dosage Frequency of Propranolol on Sleep Patterns in Patients with Infantile Hemangiomas

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Protocol Title:	Assessing the Impact of Dosage Frequency of Propranolol on Sleep Patterns in Patients with Infantile Hemangiomas.
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Sample Size:	174
Number of Sites:	Two study sites – Pediatric Plastic Surgery Clinic at the University of Texas Health Sciences Center at Houston and Dermatology Clinic at the University of Texas Health Sciences Center at Houston
Study Duration:	Three years
Subject Duration:	Up to age 18 months
Version:	1.4
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Research Question:
In patients with infantile hemangioma, does three times a day (TID) dosing versus twice a day (BID) dosing of propranolol significantly improve subjective sleep scores?

Background and Significance:
Hemangiomas are the most common benign tumors of vascular endothelium in infants and children and are the most common tumors of childhood (Darrow et al., 2017). These vascular lesions often present as a colored patch of skin within the first days to months of life and occur focally, typically on the head and neck. Hemangiomas are unique because following their growth phase is a longer involution phase. The proliferative phase presents as a rapid, disordered proliferation of vasculature that is most evident during the first three to eight weeks of life. The subsequent involution is replaced by fibrous tissue over the next 4-6 years of life (Léauté-Labrèze et al., 2017). Despite being short lived, some hemangiomas present with complications of ulceration, permanent disfigurement, or physiologic restrictions (Tanner et al., 1998). Hemangiomas near the eye can lead to permanent strabismus and astigmatism, and tracheal hemangiomas can cause life threatening upper airway obstruction (Léauté-Labrèze et al., 2017).

A variety of treatment options exist for hemangiomas including oral and topical beta blockers, systemic corticosteroids, pulsed dye laser therapy, excisional surgery, and embolization. Propranolol was approved by the FDA in 2014 for the treatment of infantile hemangiomas and has since become the first line therapy. Propranolol's mechanism in the involution of hemangiomas is through induction of apoptosis and reduction of VEGF in epithelial cells. Propranolol as a treatment is able to both block growth and cause regression of infantile hemangiomas, leading to significant increases in the complete, or near complete, involution of the hemangioma compared to a placebo (Léauté-Labréze et al., 2015). However, propranolol shows minimal effectiveness in treating hemangiomas after 18 months (Chang et al., 2017). While

rare, serious adverse effects exist for propranolol including hypotension, bradycardia, hyperkalemia, bronchospasm, and hypoglycemia (Léaute-Labrèze et al., 2016). For this reason, oral propranolol is not indicated for use in patients with existing cardiac or pulmonary disease. Additionally, sleep disturbances have been commonly reported as a side effect. Other beta blockers, such as atenolol and nadolol, have yielded promising data supporting their efficacy in the treatment of hemangiomas, with fewer side effects, but these trials have been small and limited (Bernabeu-Wittel et al., 2015). Regarding, superficial hemangiomas, topical beta blockers, like Timolol, have exhibited similar treatment outcomes as the oral form, and have resulted in fewer CNS side effects.

Prior to the FDA approval of propranolol for therapy of infantile hemangiomas, systemic corticosteroids were the primary therapy of choice for hemangiomas (Fost & Esterly, 1968). Although they have been largely replaced by propranolol, they serve as an alternative treatment modality for patients with contraindications to beta blockers. Despite the positive outcomes that can be seen using prednisone, the adverse effects of chronic steroid use may outweigh its efficacy in treating hemangiomas. Notably, the immunosuppression caused by corticosteroids increases the risk of infection in the patient and decreases the efficacy of some vaccines they are required to receive in their first two years of life (Boon et al., 1999).

In lieu of pharmacotherapy, pulsed dye lasers offer a noninvasive modality of treatment with great safety. However, they are primarily indicated for superficial hemangiomas as they only penetrate 1.2 mm (Stier et al., 2008). Excisional surgery can be used when medical treatment is unlikely to yield benefit or poses a greater risk, such as with residual scarring, noninvoluted hemangiomas, or cosmetically concerning hemangiomas. The resultant post-surgical scar may be worse than the results of a spontaneous involution. Finally, embolization has been used as a last resort treatment, but some data suggests that the results may be temporary (Mcheik et al., 2005).

Overall, oral beta blockers have been the mainstay treatment for hemangiomas, but their association with sleep disturbances has continued to frustrate parents. Propranolol exhibits strong penetration into the blood brain barrier due to its lipophilicity. This penetration is likely exaggerated by the increased permeability of the blood brain barrier in infants (Vivas-Colmenares et al., 2015). Pediatric patients are thus at even higher risk of CNS side effects such as sleep disturbance and agitation. Parent reports of sleep impairments includes nightmares, insomnia, restlessness, increased waking, and overall sleep disturbance (Xerfan et al., 2020). While these sleep disturbances may be considered a minor side effect, the issue is cited as the most common reason for early discontinuation of propranolol (Ji et al., 2018).

The standard dosing regimen for oral propranolol for the treatment of infantile hemangiomas is twice a day (BID) dosage. In our multidisciplinary vascular anomalies clinic, parents of infants on propranolol for hemangiomas are queried at each visit regarding side effects. If a parent discusses concerns regarding sleep patterns, our standard protocol is to alter the regimen to three times a day (TID) dosage. While this seems to improve the sleep symptoms, there is no evidence to support this dosing schedule. The purpose of this study is therefore two-fold:

1. Assess the baseline sleep pattern disruption for patients starting oral propranolol at the standard BID dosing regimen compared to the control (timolol) group.

2. Determine if there is a significant improvement in the sleep patterns in infants taking oral propranolol on the TID dosing regimen versus the control (timolol) group.

PICO

P: In patients with infantile hemangiomas
I: does TID dosing of oral propranolol versus
C: standard BID dosing of oral propranolol
O: result in a significant improvement in subjective sleep scores

Hypothesis:
We anticipate that patients receiving the TID dosing regimen of oral propranolol will demonstrate fewer sleep awakenings compared to the control group than the BID dosing regimen compared to the control.

Study Setting:
This is a prospective study involving patients who present to the Vascular Anomalies Clinic at the University of Texas Health Sciences Center at Houston and the Dermatology Clinic at the University of Texas Health Sciences Center at Houston. This patient population consists of patients with the diagnosis of infantile hemangioma(s).

Study Population:
Inclusion Criteria:
1. Patients with clinically diagnosed hemangiomas.
2. Age <18 months
3. English or Spanish speaking only

Exclusion Criteria:
1. Parents who do not consent to the study.
2. Significant cardiac or pulmonary disease who are unable to tolerate oral propranolol
3. Age >18 months
4. Non-English or Spanish speaking parents.

Study Design:
Prospective, single center, randomized controlled trial – parallel groups

Primary Outcome:
1. Using the BISQ, number of sleep awakenings per night between the control (timolol) group and the BID propranolol group at 6 months on therapy.
2. . Using the BISQ, number of sleep awakenings per night between the control (timolol) group and the TID propranolol group at 6 months on therapy.

Secondary Outcomes:
1. Using the BISQ, we will compare the following metrics beween the control vs BID and control vs TID groups at every 3 month interval for the total study duration (up to 18 months on therapy).
    a. Total awake time per night
    b. Qualitative assessment of difficulty falling asleep
    c. Time to fall asleep
    d. Longest sleep stretch per night
2. Clinical Response to Medication
    a. Qualitative clinical assessment on size, color changes of hemangiomas
3. Evaluation of potential side effects

Sample Size:
A sample size calculation was performed using best estimates in the literature provided by Theiler et al. (Theiler et al., 2021). Primary outcome was defined as number of awakenings per

night of sleep at 6 months of time on propranolol. In the Theiler et al study, patients on propranolol had 0.26 +/- 0.09 vs control patients of 0.21 +/- 0.1 awakenings per night. Utilizing a two-tailed analysis, we anticipate enrollment of 58 patients per treatment arm, giving our study 80% power with alpha 0.05. Given our number of annual patients (approximately 60 per year), we anticipate this study to be performed in 3 years. A concurrent Bayesian analysis will be performed.

We will analyze the data as two separate studies, each using the control (timolol) group as the reference. The BID propranolol group will be compared to the control group, as well as the TID group compared to control. This will allow us to see the effective change of sleep awakenings in each dosage group compared to control.

Research Strategy

Screening:

Patients will be identified by the primary investigator (Greives) or one of the members of the VA team (Hebert, Atkinson, Turner) during routine clinic appointments. Parents of infants with the diagnosis of infantile hemangiomas will be invited to enroll in the study prospectively. They will be given all the information regarding the study and the consent forms in clinic. All patients, including those who consent to the protocol or refuse, will follow the same protocol for therapy, but information will only be abstracted on those patients enrolled in the study.

Blinding:

This is an open label study so patients and providers will not be blinded.

Randomization:

Following enrollment and informed consent, patients will be randomized using a computer-generated randomization using permutated blocks of 6 patients. Randomization is to occur in the clinic at the time of the first prescription.

Prescription:

1. Control group: Patients with a small (<2cm) isolated infantile hemangioma are prescribed timolol 0.5% ophthalmic drops, a topical beta-blocker. Topical timolol has not demonstrated any concerns for sleep disturbances. Therefore, these patients will be enrolled as control patients in a non-randomized fashion.

Dosage for timolol 0.5% is 1 drop BID directly onto the hemangioma

2. Study groups: Patients with larger (>2cm) or multiple (>1) hemangiomas will be randomized to BID or TID dosage of propranolol. The prescription will be sent electronically to the pharmacy in the standard fashion for the practice. All patients will be initiated with the following schedule with medication administration to follow feeding:

Week 1: 0.5 mg/kg/day divided BID or TID

Week 2: 1 mg/kg/day divided BID or TID

Week 3: 2 mg/kg/day divided BID or TID. Patients will stay on this dosage until their 3 month follow up visit.

Sleep Survey:

In this study, we propose to use the Brief Infant Sleep Questionnaire (BISQ) to record and quantify caregiver reports of infant sleep. The BISQ has been validated as a multi-dimensional survey for evaluating infant sleep due to its reliability and high specificity of sleep parameters (Sadeh, 2004; Del-Ponte et al., 2020). Parents will be offered this study at each of the clinic visits (every 3 months) from the date of initial prescription until termination of the medication (18 months of age). Patients in all three groups (Timolol, BID Propranolol, and TID Propranolol) will be given this survey.

Follow up: Once a prescription is initiated, all patients with infantile hemangiomas stay on the medication until 18 months of age. Patients are seen every three months, either in person or virtual visits. During that visit, a recent weight is used to adjust their dosage of the oral propranolol to the new appropriate level. Each of these visits will be an opportunity for the sleep survey to be given.

Study Termination: After 18 months of age, all patients are removed from medication (timolol and propranolol). After this visit and final sleep assessment, all patients will be removed from the study.

Data Collection

1. Patient demographic information: name, date of birth, birth history, race, ethnicity, gender.
2. Location(s), measurements, and photos of vascular malformation(s)
3. BISQ sleep survey
    a. Timing: Every 3 months\

Safety Measures:

Patients are treated under routine clinical protocols currently in place. In over 7 years and 1000 patients, we have had NO adverse effects from the medication.

Timolol has no known side effects when administered topically to hemaniogmas.

For the oral medication, we extensively counsel our patients and parents to only give the medication after feeding to reduce the risk of post dosage hypoglycemia. We also recommend omitting a dose if the infant is not feeding, throws up after feeds, or didn't take their entire feed. We recommend holding the medication if the infant has a fever or is otherwise sick and resuming at the prior dosage once they are afebrile.

Serious adverse events would be considered for stopping the medication for routine clinical care may include the following, but would require an evaluation from one of our pediatric team members:
1. New diagnosis of congenital cardiac anomaly
2. Hospitalization for hypoglycemia
3. Hospitalization for hypotension

As this entire protocol is currently employed in our clinic as standard of care, except for the survey questionnaire, we will not be forming a DSMB. This study represents no elevated risk over routine clinical care thus does not pose any additional safety burden on the patients of their families. The only burden is the extra time in clinic needed to take the survey.

Human Subjects Research

Risk to subjects

Patients included in this study will only change the timing of their dosage in their treatment course. The medical risk of substituting a TID dosing regimen for a BID regimen is minimal.

Potential Benefits

While no direct benefits will extend these patients, this information will benefit future patients as we will have more information regarding the potential sleep benefits of alternative dosing of propranolol in the treatment of hemangioma. This will benefit the entire scientific community as well considering this information is not currently documented in the literature.

Ethics

There are not ethical conflicts involved in this study. All medical management will proceed with our current standard of care, which will be provided to the patients regardless of inclusion/exclusion in the study.

Consent

Participating clinicians will identify patients with hemangiomas when they present for their initial evaluation to the Pediatric Plastic Surgery clinic or Dermatology clinic at the University of Texas Health Sciences Center at Houston. Parents of the patient will have the purpose of the study described to them prior to being provided with informed consent by either the Principal Investigator or research staff. Time will be given to the parents to agree to participate in the study via the consent form and ask any questions prior to the patient's participation.

Confidentiality

Research data will include any personal health information that can be used to identify the patients. All medical records are imported directly into the EPIC system, including prescriptions and patient photos. BSIQ Sleep records will always be kept on a password locked computer in the Principal Investigator's locked office and information will be transcribed into a Redcap database that has been created for this study using the UTHealth platform. Release of information will only occur with de-identified data for research purposes. Patient information will only be accessible via the University of Texas Health Science Center at Houston's encrypted file sharing program. This program will not allow the data to be downloaded, only viewed.

Cost/Payment

There will be no direct cost to the patient/parent as part of this study. No additional costs will be incurred by entering this study as this is standard of care for all our current patients for the medication itself. There is no cost to the parents for using the sleep questionnaire. There is no payment to parents/patients for their participation.

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