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The response pattern and adherence to oral propranolol among Saudi children treated for infantile hemangioma

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Abstract

Background: Although the role of oral propranolol in treating IH is now well-recognized worldwide, the variation of treatment effectiveness over time and patients adherence have not been documented among Saudi.

Objective: To identify the variation of effectiveness over the treatment period and the adherence to treatment of oral propranolol among Saudi children treated for infantile hemangiomas (IH).

Patients and methods: Children presented for treatment of problematic IH between February 2012 and September 2015 were recruited in a prospective observational study of oral propranolol at 2 mg/kg/day. Data about patients' adherence (categorized based compliance with the scheduled visits and treatment administration), lesion comparative response score (based on the relative improvement compared to previous visit) and possible side-effects were collected during follow-up. Treatment was stopped once the lesions failed to show significant improvement. Serial digital photography was used for response and final outcome assessments.

Results: Thirty-six cases were enrolled at a median (range) age of 6 (2–55) months. Cases were classified as 19 minor and 17 major, including 10 with ulcerations. Adherence was poor in 12 (33.3%), moderate in 4 (11.1%) and good in 19 (52.8%). Excluding the poorly adherent, the mean duration of treatment and follow up were 6 ± 3.4 and 7 ± 4.6 months, respectively. A mean comparative response score of 1.67 from a maximum of 2 was achieved during the first month of treatment, then gradually diminished reaching 0.19 and 0 at 8 and 10 months respectively. Patients who successfully completed 6 months of treatment ($n = 19$) were more likely to present with major lesions (68.4% vs. 33.3%, $P = 0.047$) and at an earlier median age (4 vs. 11 months, $P = 0.018$). Complete or near complete responses was 47% achieved. All ulcerated lesions healed at a median of 2 (1–4) months.

Conclusion: The most dramatic response to treatment appeared during the first month, then progressively diminished toward negligible benefits beyond 8 months. Adherence to treatment can pose a challenge to achieving satisfactory outcomes.

Keywords: Hemangioma; Propranolol; Duration; Response; Adherence; Ulcerating

1. Introduction

Infantile hemangiomas (IHs) are very common benign vascular tumors present early in life in about 5–10% of infants and characterized by a period of rapid growth followed by gradual involution (Drolet et al., 1999; Frieden et al., 1997). Despite its major drawbacks in children, oral steroid has been the main effective treatment for problematic hemangiomas (Bennett et al., 2001) until the first observations made by Leaute-Labreze et al. (2008) of the

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effectiveness of oral propranolol in accelerating IH involution, since it has largely replaced all other treatment modalities to become the treatment of choice (Drolet et al., 2013).

The effectiveness and safety of propranolol has been well-demonstrated in many retrospective (Marqueling et al., 2013) and prospective studies (Janmohamed et al., 2015; Chang et al., 2015), including many randomized trials (Leaute-Labreze et al., 2013, 2015; Hogeling et al., 2011). However, the variability of its effectiveness over the treatment period and the optimal treatment duration have not been described among a Saudi population. Moreover, Saudi patients' adherence to the treatment regime, which is known to be problematic among children with chronic illnesses, has yet to be addressed.

Here we performed an observational prospective outpatient-based study to document the relative effectiveness of a propranolol protocol for treating children with IH, focusing mainly on describing the patterns of lesion response over time and patients' adherence.

2. Patients and methods

2.1. Patients

All patients referred to our clinic at King Saud University Medical City with problematic IH between February 2012 and September 2015 were enrolled in a prospective study to assess the effectiveness, response pattern, side-effects and compliance of our propranolol treatment program. The study is approved by our local IRB at King Saud University College of Medicine (project number E-15-1737). The eligible patients were all children younger than 8 years-old, who presented with problematic IH causing disfigurement, ulceration, pain or compression to nearby structures. The exclusion criteria were; children younger than one month of age, previous propranolol therapy, history of congenital heart diseases and PHACE syndrome or significant respiratory illnesses requiring continuous medication use. Due to the accumulated evidence on the safety of propranolol for treating IH, our pre-treatment screening was limited to a pediatrician referral for general exam, assessment of blood pressure, heart rate, blood sugar and performing an electrocardiogram.

2.2. Treatment

In our protocol, the propranolol total targeted dose (TTD) was 2 mg/kg/day divided into two equal doses. Patients were instructed to start at 70% of the TTD and to add 10% of the TTD every two days, until reaching 100% within a week. During the subsequent visits, the doses were adjusted as the child gained weight. Care givers were instructed to report a list of possible side-effect symptoms, including: changes in feeding, sleeping and bowel movement patterns, change in activities and worsening respiratory symptoms. The first visit was scheduled at two weeks after treatment and was limited to treatment tolerance and initial compliance assessment. The first treatment response evaluation visit was scheduled at 1 month after starting treatment, with subsequent visits scheduled every 2 months.

To assess the ideal treatment duration and its long-term effectiveness, we did not specify a treatment period, however, care givers were informed that they have the choice to stop treatment after 6 months if the lesion is stabilized without progressive improvement over any subsequent two-month treatment interval.

2.3. Classification and response assessment

To assess treatment response, sequential digital photographs were taken during each visit and stored in each patient's electronic database. To date, there is no universal consensus on the ideal IH severity and activity scoring system, as most published literatures describe various endogenously developed scoring schemes. Generally, most hemangioma activity evaluation scoring systems are based on the size, depth, color and ulceration, (Janmohamed et al., 2015; Schneider et al., 2014) while in assessing the lesion severity additional factors are considered to indicate higher severity, such as facial location, compression and associated pain (Haggstrom et al., 2012).

We have adopted a simplified hybrid scoring system based on the above cited criteria. The lesions were simply classified into major or minor, where major lesions include: any facial lesion >2.5 cm, body lesions >5 cm, as well as ulcerating, painful, markedly raised (>3 cm) lesions or lesions causing compression to adjacent structures. Final response was recoded at the last visit for patients who completed at least 6 months of follow-up and was based on the definition of complete or near complete resolution described by Leaute-Labreze et al. (2015). A simplified comparative sequential response scoring is adopted by comparing the change in color, size and ulcer status of each visit photo in relation to the previous visit (Fig. 1). Because of the natural tendency of hemangioma to improve spontaneously, a scale of zero was assigned if there was either a minimal or no change.

The sequential responses scoring and final outcome were based on the average evaluation of three independent physicians who are experienced in treating skin lesions. Each was separately asked to view the patient's serial photographs and record their assessment based on our scoring system. An example of the sequential response scoring scheme is shown in Figs. 2 and 3.

Patients' adherence to propranolol treatment was assessed at each follow up visit based on two elements; adherence to the scheduled clinical visits and parents commitment to administer the recommended propranolol doses. It was categorized into three major categories; good adherence (those who took the recommended dose and followed-up for at least 6 months), moderate (those who decided to stop treatment or lost follow-up after 2 months) and poor (for the remaining cases).

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