CASE REPORT

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Treatment of infantile hemangioma: case report

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ABSTRACT

Background: Although benign in origin, infantile hemangiomas can occasionally cause lifelong deformity, functional disability, and even life-threatening consequences. As a result, therapy is favored above an active observation plan. When treating infantile hemangiomas at high risk, the first line of therapy should be systemic propranolol. While oral propranolol is generally regarded as a safe and effective medication, it is important to consider potential adverse effects. Further research and evidence-based practices are needed to improve clinical results.

Case report: Here, we describe a 3-month-old child who had an infantile hemangioma and how oral propranolol significantly improved the lesion. The patient's mother takes her to the hospital when she notices a reddish mass that extends from her nasal bridge to her right cheek. After three days, the patient's red mass had lessened. The kid was monitored in the clinic for three hours following the initial increase in propranolol dosage, which was raised to 2 mg/kg/day. Every week, the patient was monitored at the clinic. The child's weight had climbed to 7 kg after 4 weeks, and she had no side effects from an increased propranolol dosage.

Conclusion: A critical factor is the early diagnosis of at-risk infantile haemangiomas, which calls for pediatricians, general practitioners, and health visitors to be more alert in order to spot potentially troublesome infantile haemangiomas in the first two to three weeks of life.

Keywords: infantile hemangioma, oral propranolol, treatment.
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BACKGROUND

The most common tumor of infancy, infantile hemangioma (IH), affects 4–10% of babies in their first year of life. IHs typically appear within the first few weeks of life, expand promptly during infancy, and, in the majority of cases, spontaneously dissipate in early childhood with no serious consequences.[1] An aberrant cluster of tiny blood vessels that develops throughout the first year of life is what causes IH. Infants who are Caucasian are more likely than other racial groups to develop IHs. Additionally, there is a female majority with a female to male ratio of up to 5:1. Hemangiomas can also form in newborns who are premature, have low birth weights, or have prenatal hypoxia. IH risk increases 25% for every 500-g reduction in birth weight and affects 25% to 30% of infants <1000 g.[2] Infants with older mothers tend to acquire IHs. IHs typically occur sporadically, but they have been observed to run in families. They have been linked to an autosomal dominant inheritance pattern. An increased frequency of IHs is linked to two syndromes: PHACE syndrome and LUMBAR syndrome.[3]

IH is typically treated with pharmacotherapy, specifically adrenergic β-blockers. Because it is widely accessible, efficient, and secure for use in pediatric patients, oral propranolol is the drug of preference for systemic IH therapy. In addition to IH properties, patient risk factors, and family preferences, treatment choices, product selection, and route of administration are tailored to each patient. Longer therapy sessions and early intervention improve successful long-term outcomes in IH. For uncomplicated IH, the prognosis is excellent, and most patients experience complete involution. In 5 years, 50% of hemangiomas will go away, and in 9 years, 90%. About 8% of IH result in aesthetic deformities and need intervention.[4]

CASE PRESENTATION

A 3-month-old girl's mother takes her to the hospital because she has a reddish-colored mass on her nasal bridge that extends to her right cheek. This lump did not exist at birth, but it began to form at 3 days of age, starting as a little crimson dot and growing in size over time. The parents took her to several doctors however did not receive any specific treatment. The lump was painless without any bleeding. There is a history of hemangioma from the mother's cousin. Everything was normal during pregnancy. The patient was a first born. She was born via vaginal delivery, full-term with birth weight of 3000 gr and birth length of 49 cm. There was no complication during labor. There is no previous history of illness or any drug allergy.

On physical examination, she was active. The patient was 5,6 kg at examination. We observed multiple

bright-red lumps on the nose bridge, near medial canthus of the right eye extending to the undereye and right cheek. There is no lump found on another site and the rest of examination revealed normal results.

After consultation, it was decided to begin treatment with oral Propranolol. Vital signs were kept monitored. Comprehensive evaluation showed normal results and ECG screening showed a normal sinus rhythm. Starting on day I, oral propranolol was administered at 0.5 mg/kg, then on days II, III, and IV at 1 mg/kg, 1.5 mg/kg, and 2 mg/day. Parents were instructed to report any clinically apparent hypotension, bradycardia, or hypoglycemia—signs of treatment complications. Hypotension can also manifest as lethargy. Additionally, parents were told to discontinue administering Propranolol if there is no food intake and to administer the drugs with food.

Outcome and follow-up

After three days, the patient's red mass had lessened. The kid was monitored in the clinic for three hours following the initial increase in propranolol dosage, which was raised to 2 mg/kg/day. Every week, the patient was monitored at the clinic. The child's weight had climbed to 7 kg after 4 weeks, and she had no side effects from an increased propranolol dosage. After that, the patient was checked on every month to ensure that the face haemangiomas were disappearing, involution, and continuing weight increase. Her propranolol dosage has been reduced off around 4 years following therapy, coinciding with the haemangiomas' disappearing. The haemangioma flattens and leaves a thin scar on the face as it involutes, losing its vibrant red color (Figure 1).

Figure 1. Hemangioma lesion at 3, 4, 5, 6 months old, 1 year, 4 year and most recent photos; showing significant improvement of the lesion.

Differential diagnosis

The diagnosis of IH is made mostly on the basis of clinical presentation; imaging is rarely required. This category includes a large number of differentials related to hemangiomas. It is necessary to distinguish IHs from other vascular cancers. Congenital hemangiomas, on the other hand, are produced by mutations in the GNAQ and GNA11 genes and are present from birth, albeit they are secondary to cellular hyperplasia. There are three further categories for congenital hemangiomas: fast involuting, non-involuting, and partially involuting. Congenital hemangiomas are diagnosed when there is no GLUT1 staining present, despite the fact that some may mirror the normal cycle of IH. Another class of vascular abnormalities are vascular malformations, which are often present at birth, do not exhibit growth, and may even regress spontaneously. They are produced by faulty vascular morphogenesis (Table 1).[5]

IHs can be identified from other children cancers by their characteristic life cycle and vivid red skin blemishes.[6] IHs can be seen at birth as reddish macules or mild telangiectasias, but by the time they are two to three weeks old, they usually begin to multiply and become noticeable. Deep IHs are blue-colored, affect subcutaneous tissues, and occur later than surface lesions. Growth occurs quickly during the proliferation period, which spans from the first few weeks of life to four or six months.[7]

Treatment

Preventing potentially fatal complications and permanent disfigurement, lowering psychosocial stress for the patient and family, and avoiding needless interventions are the goals of IH treatment. Risk of life-threatening complications, ulceration, and permanent scarring are indications for IH treatment. For patients with complicated, high-risk IHs or associated syndromes, early intervention between 4 and 6 weeks of age may be able to prevent IH complications.[8]

For uncomplicated lesions, conservative, non-pharmacologic management with active monitoring is appropriate. By the age of 12 months, IHs

Table 1. Difference between vascular malformation and IHs[5]

Features	Infantile Hemangiomas	Vascular Malformation
Age of emergence	Often after birth	At birth
Proliferation	With a rapid proliferation phase	Growth with the body development
Involution	Yes	No
Epidemiology	Female domination (3:1)	No prevalence
Risk factors of expansion	None	Hormone changes, trauma, infections, and so on
Physical examination	Palpation of a solid mass	Palpation of thrill or pulsation, auscultation of vascular murmur
Diagnosis	Based on medical history and clinical manifestation	Based on medical histroy, clinical manifestation and imaging examination
Treatment	Most of the His can involute before 4 years old. The higher risk ones need oral propranolol intervention, laser or surgey	The symptomatic ones need treatment such as slereotherapy, surgery or laser

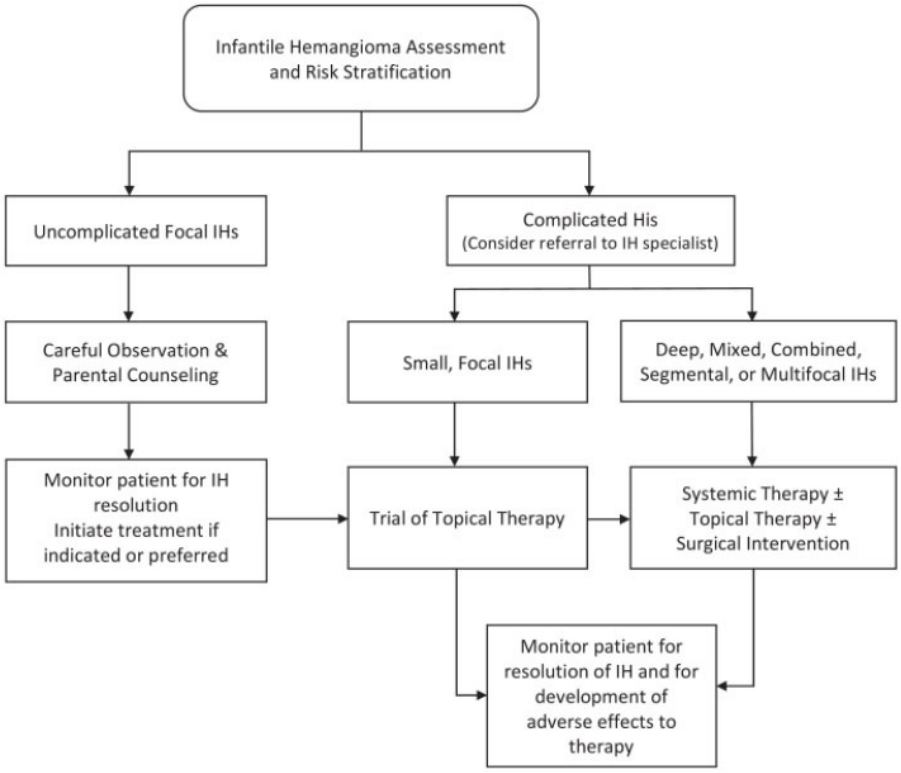

Figure 2. Infantile hemangioma (IH) intervention algorithm.[9]

typically start to involute on their own without treatment. Pharmacotherapy shortens the time it takes for involution to complete and speeds up IH proliferation. Surgery and laser therapy are only used when pharmaceutical treatments have failed or to treat after-involution side effects.[8] IH intervention algorithm is showed in Figure 2.

The cornerstone of IH treatment is pharmacotherapy. IH management may involve local, systemic, or a combination of treatments. B-blockers are advised as first-line treatments for IH due to their high efficacy. Most patients are advised to use oral propranolol due to its efficacy and safety. Topical β-blockers are used both alone and in conjunction with systemic therapy to treat IH.[2]

Patients with thin, superficial focal IHs and those for whom systemic therapy is contraindicated are advised to receive topical therapy. To reduce systemic side effects, topical therapy can be used in combination therapy plans. The preferred topical agent is timolol maleate. Timolol has a similar mechanism of action to propranolol as a non-selective -antagonist. Topical β-blockers reduce angiotensin II levels on the surface of the hemangioma by acting locally through the renin-angiotensin system, causing IH regression and eventual resolution. FDA-approved gel-forming solutions (GFS) and 0.25% and 0.5% ophthalmic solutions of timolol maleate are commercially available for the treatment of elevated intraocular pressure in both adult and pediatric patients. Due to the possibility of systemic absorption, topical timolol shouldn't be used on mucous membranes or areas that are infected with ulcers.[2]

According to FDA, topical timolol maleate is contraindicated in patients with asthma, bradycardia, second- or third-degree heart block, and cardiogenic shock. Timolol topical therapy is well tolerated, and no specific monitoring is required. If timolol topical is unsuccessful, systemic IH therapy ought to be started. Timolol is better than cautious waiting for treating babies with superficial IH in high-risk locations. Patients on timolol showed a notably lower number of problems compared to the control group. Lips are considered a high-risk area for ulceration in people with IHs. Research has shown that oral β-blockers are more successful in treating lip IHs than topical timolol treatment. Oral propranolol, although exceedingly safe and effective, is not always sufficient for IHs of the lips; in almost all instances, systemic propranolol was needed before further therapy could be started. Topical timolol has been reported to be an effective treatment for complex IH in newborns.[10]

Topical propranolol appeared to be less effective but safer than oral propranolol in individuals with tiny superficial hemangiomas, when the cosmetic or asymptomatic effects did not need oral

Table 2. Propranolol medication counseling[9]

General counseling
• Administer during or after feeds • Admminister during daytime hours • Administer directly into the infant's mouth or mix with small amount of milk, formula, or juice • Provide frequent feeds (every 3-4 hr in infants <6 wk, every 5 hr for infants 6 wk to 4 mo, and every 6-8 hr for infants > 4 mo) • Omit dose(s) if infant is refusing feeds or feeding less frequently • Omit doses(s) if infant is ill or experiencing respiratory symptoms • Administed doses at least 8 hr apart • If a dose is missed, give the dose as soon as remembered as long as it is after a feed and the next-scheduled dose is at least 8 hr away • Do not double up or increase doses to make up missed doses • If the infant spits out the dose, do not repeat it; give the next dose at the scheduled time • Propranolol 4.28 mg/mL oral solution: date the box when the bottle is first opened and discard after 60 days; do not shake before use • Do not abruptly discontinue therapy without physican advice; medication should be decreased slowly to avoid adverse effects
Common adverse effects
• Sleep disturbances (falling asleep, staying asleep) • Gastrointestinal problems (diarrhea, vomiting) • Irritability, agitation, nighmares
Seek immediate medical attention for any of the below serious adverse reactions
• Low blood sugar (hypoglycemia): sweating, shakiness, increased drowsiness or irritability, poor feeding, pale skin color, low body temperatures, seizures • Low HR (bradycardia) or low BP (hypotension): pale skin color, slow or uneven heartbeats, cool or cold extremities, blue skin color, or fainting • Breathing problems (bronchospams): breathing difficulties or wheezing

propranolol therapy. When topical propranolol was utilized as the first-line therapy for IHs in more than 600 individuals, a comprehensive evaluation of 12 trials showed no indication of any systemic adverse effects. Propranolol preparations include creams, unguents, and gels manufactured from galenic formulations with a concentration of 0.5% to 5%; treatment durations varied from 2 weeks to 16.5 months. 90% of the time, using topical propranolol improved the lesion's condition and at least 50% of its size was decreased.[11]

Systemic and intralesional corticosteroids were the mainstay of IH treatment before the adoption of β-blockers. Corticosteroids cause IH resolution by non-specifically reducing inflammation. Corticosteroids have significant adverse consequences both short- and long-term, including as growth inhibition, hyperglycemia, weight gain, behavioral issues, immune system and adrenal suppression, and hypertension.[12,13] Only patients who fail to respond to β-blocker therapy or who experience intolerable side effects should be prescribed corticosteroids. Aly et al investigated the efficacy of a 2-week regimen of propranolol alone or in combination with corticosteroids. Early in therapy, at 2, 4, and 8 weeks, the authors found statistically significant improved response with the combination treatment regimen; however, at 6 months, the superior response was no longer noticeable.[14]

Comprehensive parent and caregiver education should cover dosage instructions, potential side effects, indications of hypoglycemia and bradycardia, and a sick-day strategy for delaying doses when the child is unwell.[9] Propranolol medication counseling is showed in Table 2.

Since the development of the notion of selective photothermlysis, laser treatment has been used extensively to treat cutaneous lesions, including IHs. The laser that is most commonly used to treat IHs is the pulsed dye laser (PDL). Similar to propranolol, it has been shown that PDL therapy dramatically reduces VEGF levels in the patients' sera. During the proliferative phase of IH development, laser therapy is not recommended due to its ineffectiveness and potential for consequences. In terms of aesthetic results, the group that received laser treatment fared better than the observation group; there was greater color fading and a quicker halt of the proliferative phase of development.[15]

The Nd:YAG laser is the second most often used kind of laser to treat vascular lesions. Its light emission occurs in the mid-infrared, which is corresponding to the extra infrared absorption peak of oxyhemoglobin at around 1000 nm. Since Nd:YAG laser penetrates deeper than PDL, it is suggested for the treatment of deep or mixed hemangiomas, particularly when combined with both types of lasers. It was discovered that combining Nd:YAG/PDL laser treatment with systemic propranolol was a safe and efficient way to treat IH. There were fewer adverse effects, but the course of therapy did not seem to be shortened. On the other hand, recent research by Sugimoto et al. suggested that the propranolol plus PDL combination may shorten the time that propranolol is administered. In a double-blind, randomized controlled experiment, PDL laser with timolol gel was superior than PDL alone, but only if the treatment was initiated after the child became three months old.[15]

DISCUSSION

Infancy-related IHs are the most prevalent benign vascular tumors, affecting up to 5% of infants. Until one to two weeks after delivery, IHs usually go undetected or appear as a mild discoloration with a faint halo. Eighty percent of IHs appear in the face and neck region. When highly localized IHs are present, they manifest

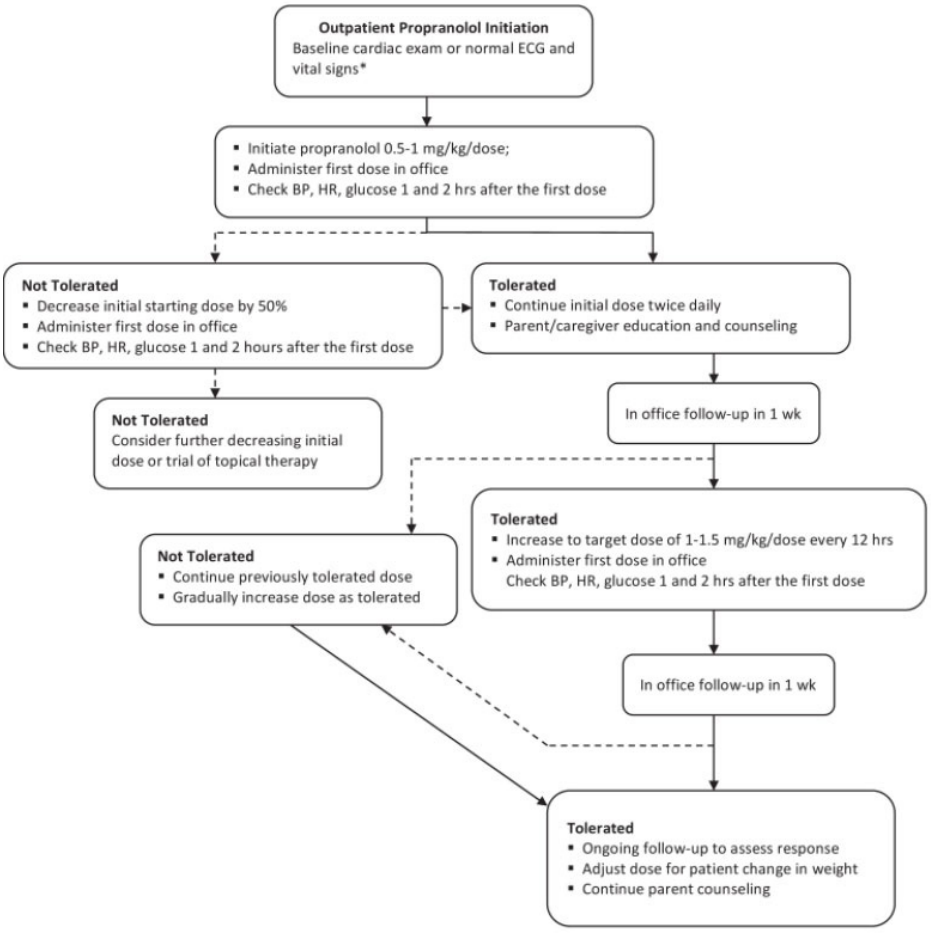

Figure 3. Outpatient propranolol initiation.[9]

as blue tumors with fuzzy edges, and diagnosis may not come until three months after delivery. There are three stages in an IH's natural cycle. First, there is the early proliferative or growth phase, during which the lesion grows at its quickest rate between 5.5 and 7.5 weeks while remaining stable and quiescent for several months (between 6 and 12 months of life). Second, the plateau phase lasts for many months, during which the lesion is stable and dormant (between 6 and 12 months of life). Third, involution phase: the color transitions from brilliant red to purple or gray, and the regressive IHs become softer and more compressible. Though there are frequently lingering alterations, the skin may return to normal.[16]

This appearance is consistent with our case, in which a 3-month-old girl is brought to the hospital with a reddish-brown tumor that extends to her right cheek from the bridge of her nose. This lump did not exist at birth, but it began to form at 3 days of age, starting as a little crimson dot and growing in size over time. Based on the extent of soft tissue involvement, IH generally classified as superficial, deep, or mixed. Deep IHs extend into the subcutaneous tissue, superficial IHs involve the skin surface, and mixed IHs exhibit qualities of superficial and deep His. More specifically, IH can be classified according to anatomic arrangement into focal, multifocal, segmental, or indeterminate. Focal IHs are well-defined lesions that appear to originate from a central focal point. Multifocal IHs are focal lesions that involve multiple anatomic sites. Segmental IHs involve extended areas of skin in a plaque-like manner in patterns of embryonal developmental units.[17] We observed multiple bright-red lumps on the nose bridge, near medial canthus of the right eye extending to the undereye and right cheek. There is no lump found on another site.

Gender, age, soft-tissue depth, clinical appearance, and results all showed significant disparities. Compared to men, females were more frequently impacted. similar to the patient's current situation, who is a woman. A greater risk incidence was correlated with younger age. In the high-risk and medium-risk groups, the locations with the highest occurrence were the head and neck, while the lowest incidence was found in the low-risk group's trunk. Low risk also exhibited a greater prevalence of superficial soft-tissue depth than did high risk and medium risk.[18]

The placental origin idea is the most plausible explanation for the pathophysiology of IH. This idea states that disruption of the placenta prior to or during delivery results in the production of placental-derived endothelial progenitor cells (EPCs). These EPCs travel until they come into touch with ideal development circumstances, during which time they move and proliferate under the influence of both extrinsic and intrinsic stimuli. Dysregulation of angiogenesis and vasculogenesis are intrinsic variables that contribute to many pathways leading to the creation of IH from EPCs. On the other hand, external variables are believed to provide an environment that is conducive to the genesis of IH and include tissue hypoxia and disruptions in the developmental field.[19]

In patients older than five weeks, oral propranolol is the first-line systemic therapy for proliferating IHs. Leaute-Labreze et al. originally reported on the drug's effectiveness in 2008. Additional case reports, clinical reviews, and trials with a placebo all support the effectiveness of propranolol in treating IH. Although its exact function in IH resolution is unknown, propranolol is thought to contribute by inducing a stop in IH growth. Some of the suggested mechanisms of action for IH growth arrest include vasoconstriction, blocking of basic fibroblast growth factor and vascular endothelial growth factor communication, suppression of nitric oxide synthesis, modulation of the renin-angiotensin system, and direct cellular death.[1]

Propranolol is a lipophilic, non-specific β-receptor antagonist with variety of adverse effects, including bradycardia, wheezing, and drowsiness. Agitation and sleep disturbances are two additional adverse impacts on the

CNS. The consequences on the CNS are typically transient and infrequently requiring treatment. Treatment with propranolol could result in serious adverse reactions, such as hypoglycemia, bradycardia, and hypotension. Hypoglycemia mostly affects older patients and is not dose-related. β-blockers may mask features of hypoglycemia where diaphoresis may be the only symptom shown prior to the onset of severe hypoglycemia. To prevent hypoglycemia, propranolol is only given during or right after feedings and not when oral intake is at its lowest. Guidelines for IHs do not advocate routine glucose monitoring after treatment begins.[19]

Visceral hemangioma is one of the conditions for which propranolol is prescribed; untreated cases of this condition have an 81% mortality rate. Initiation of propranolol can be performed as a routine outpatient procedure in healthy newborns >5 weeks of corrected gestational age. Guidelines for IHs suggest starting propranolol inpatients for patients of all ages. Prior to starting propranolol, a cardiac exam or ECG should be performed. ECG screening was performed with a normal sinus rhythm. Routine cardiovascular monitoring is not recommended once normal baseline measurements are obtained. The starting dose of propranolol for the treatment of hemangioma is 0.25 mg/kg/day, and it is progressively raised to the goal dose of 2 mg/kg/day. The total daily dose can be divided 3 times daily to increase tolerance. The dose should be adjusted for patient weight gain during treatment to maintain the target dose. The dose should be weaned slowly to avoid rebound tachycardia and hypertension. During the course of a month, propranolol can be stopped by reducing the dosage for two weeks, then halving it once more for two weeks, and so on.[20]

In accordance with this advice, the patient was prescribed oral propranolol, which was begun at 0.5 mg/kg/day on day I, 1 mg/kg/day on day II, 1.5 mg/kg/day on day III, and then 2 mg/day. Parents were trained to report any adverse effects, including hypoglycemia, bradycardia, and hypotension, which can manifest clinically as lethargy. Due to the possibility of hypoglycemia, parents were also advised to discontinue providing Propranolol if no food was consumed and to provide the drugs with food.

A series of cases, including a 3-month-old boy who arrived with a mass on his right palpebral region two weeks after birth and a 4-month-old girl who presented with a fast expanding mass on her left cheek three weeks after birth, provided support for this therapeutic method. Propranolol was started at 0.25 mg/kg/day and gradually raised to 2 mg/kg/day for both patients. After two to three months, a significant decrease was seen.[21] Outpatient propranolol initiation is showed in Figure 3.

Among complications of IH, 20-40% of them are potentially life-threatening. Patients with hemangiomas under 5 cm were 32 times more likely to develop complications than those with lesions, according to a retrospective study by Akcay et al. The prognosis for simple IHs is excellent. Most IHs only have minor cosmetic effects and resolve spontaneously at roughly 4 years old.[9]

Up to 20–40% of people may experience a recurrence after stopping their medication. Female gender, tumor size > 50 cm^3, head and neck location, deep or mixed type hemangioma, and early treatment discontinuation are risk factors for IH recurrence. Resuming therapy and extending treatment duration are the methods used to manage IH recurrence. According to Kagami et al., patients with IH should continue to be observed for up to six months beyond the end of their therapy.[22]

Because of its possible negative effects, particularly on the central nervous system, propranolol should only be used in extreme cases. It should also be continued until IHs are completely involuted. Recurrence may be associated with early propranolol cessation; however, the phrase "recurrence" is not well defined; others describe it as the conspicuous regrowth of an original lesion and profuse blood flow as identified by color Doppler ultrasonography. The dosage of propranolol should be discontinued based on the post-treatment lesion regression rate. The achievement of full regression is the optimal moment to stop taking propranolol. This study's shortcoming is that we didn't assess the patient's short-, mid-, and long-term propranolol adverse effects. Nonetheless, this patient's result is noticeably good.[23]

CONCLUSION

The first-line treatment for IHs patients is propranolol, which has amazing results. Propranolol is widely accessible, safe to use, and should be discussed with parents. Our clinical experience led us to start the oral propranolol at 0.5 mg/kg/d. In order to monitor the newborns' overall condition following intervention, the initial drug should be administered in a hospital. In order to treat infantile haemangiomas while they are still in the early stages of proliferation, paediatricians, general practitioners, and health visitors must be more aware of the importance of early detection of at-risk infantile haemangiomas. These haemangiomas should be identified within the first two to three weeks of life.

DISCLOSURES

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This work is not receiving any outside support.

Conflict of Interest

There is no conflict of interest in this work, according to all of the authors.

Author Contribution

Each author participated to this study and made equal statements.

Ethical Consideration

The patient has provided informed consent and has agreed to this writing.

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