ORIGINAL ARTICLE

Oral Propranolol in the Treatment of Cutaneous Infantile Hemangioma in Children: A 3-Years Retrospective Study

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Background: Infantile hemangioma is the most common vascular tumor in children. The primary pharmacological agent currently utilized for its treatment is propranolol, which demonstrates efficacy and minimal and non-severe side effects.

Objective: To investigate the therapeutic outcomes and adverse effects of orally administered propranolol in the treatment of infantile hemangioma. Additionally, to explore patient data regarding disease manifestations and progression.

Material and Methods: Retrospective data collection from medical records of patients diagnosed with cutaneous infantile hemangioma and treated at the National Children's Health Institute for a duration of three years, between January 1, 2018 and December 31, 2020, was done.

Results: The present study included 180 patients with infantile hemangioma. The male-to-female ratio was 1 to 2.3. The median age at diagnosis and treatment initiation was four months, ranging from 1 week to 18 months. Premature infants accounted for 28 cases (15.6%). The most common locations were the head, face, and neck with 67.8%, trunk with 16.1%, and limbs with 16.1%. The most prevalent complications were ulcerations for 12.2% and visual field defects for 0.6%. The average duration of propranolol treatment was 13.01 months. Favorable response was noted in 173 patients (96%) at the 2-week follow-up. By the 6-month follow-up, all patients exhibited positive treatment responses. Adverse effects were reported in two cases, including hypoglycemic seizure and irritability.

Conclusion: Oral propranolol demonstrates favorable outcomes in treating infantile hemangioma. However, vigilant monitoring for severe adverse effects, particularly hypoglycemia-induced seizures must be done. Guardians must be informed and deeply concerned not to administer propranolol on an empty stomach, in the presence of poor feeding, or in poor physical condition.

Keywords: Oral propranolol; Infantile hemangioma; Adverse events; Hypoglycemia

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Infantile hemangiomas (IHs) are the most common benign tumors of infancy, occurring in up to 5% of children[1]. They are well-known for their unique disease progression and their spontaneous regression. The majority of IHs are not present at birth. They often appear in the first few weeks of life. The mean age at the symptoms present was one week of life as pale, telangiectatic or faint red patches. Then, they grow progressively in the first three to six months of life until nine to twelve months of age, at which time the growth rate will gradually decelerate. Involution typically begins by the time the child is a year old[2].

Regarding their spontaneous involution, some may not require treatment. Nevertheless, approximately 10% of IHs require treatment during the proliferative phase[3,4], in high-risk cases, PHACES and PELVIS can cause serious morbidities and mortalities. PHACES syndrome include posterior fossa malformations, hemangioma, arterial anomalies, coarctation of the aorta and other cardiac defects, eye abnormalities, sternal clefting and/or a supraumbilical raphe, while PELVIS syndrome include lumbosacral area hemangiomas, malformation of the external genitalia, urinary tract abnormalities with kidneys and bladder, malformations of the end of the spinal cord and abnormalities of the anus, diffuse neonatal hemangiomatosis (DNH), airway hemangioma, periorbital hemangioma or painful ulceration during the proliferative phase, In these cases, the treatment was aimed at treating a life-threatening condition, preventing morbidities and preserving vital organ

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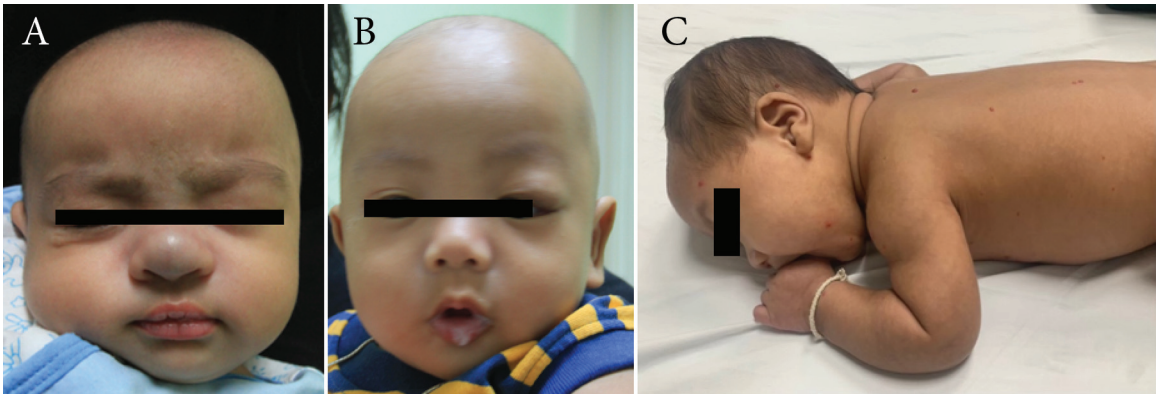

Figure 1. (A) Disfigurement: hemangioma on the tip of nose, (B) Astigmatism: hemangioma on left upper eyelid, (C) Diffuse neonatal hemangiomatosis: multiple hemangiomas with hepatic hemangioma.

function. Cases of hemangioma where IHs have reached the involution phase can still leave permanent residual[3,4] such as fibrofatty changes, telangiectasia, atrophic wrinkling, discoloration, and scarring. Disfigurement is one of the major concerns especially on the face, tip of the nose or the lips (Figure 1). Therefore, the treatment is to prevent disfigurement and improve quality of life[5,6].

Oral propranolol is currently a first-line therapy for IHs. Propranolol is a non-selective beta-blocker released in 1964[7]. The first report using oral propranolol in patients with IH was published by Léauté-Labrèze et al. in 2008, which showed a high efficacy in controlling the growth of IHs[8]. In studies, oral propranolol at standard dose of 2 mg/kg/day has excellent effects and is well tolerated[4]. However, it should be used with caution for the first several doses because of the chance of potential side effects, including bradycardia, hypotension, fatigue, bronchospasm, hypoglycemia, or even serious adverse events including cardiac arrest, severe hyperkalemia, and hypoglycemic coma[2,9,10].

The authors' aim was to assess the use of propranolol in the past three years at Queen Sirikit National Institute of Child Heath according to the efficacy and safety of propranolol in the treatment of IHs of the patients.

Material and Methods

The present study was a retrospective study aimed to investigate and compile data on patients diagnosed with cutaneous IH based on medical records at Queen Sirikit National Institute of Child Health between January 1, 2018 and December 31, 2020. One hundred eighty cases were included in the analysis.

Patients were assessed every one to two months after initiation of treatment. Criteria for therapy response included a decrease in the intensity of color and volume by either visual assessment of changes in IH color and size in clinic visits or serial photographs. The authors reviewed demographic data including age, gender, type and, location of IHs, dose, duration, treatment outcome and complications of oral propranolol. Statistical analysis to data, represented as percentages.

The present study was approved by the research ethics review committee of the Queen Sirikit National Institute of Child Health (REC.051/2564).

Results

One hundred eighty patients were included, with 126 cases (70%) were female and 15.6% of patients were premature infants. They started to have the symptoms with a mean age of one week and a range of 0 to 9 months. Pre-existing medical conditions were presented in eleven cases (6.1%), including cow's milk protein allergy with dermatitis in three cases, glucose-6-phosphate dehydrogenase deficiency in three cases, congenital heart disease in two cases, history of intracranial hemorrhage in one case, and hypothyroidism in one case.

The subtypes of IHs included superficial type in 74.4%, deep type in 16.7%, and mixed type in 8.9%. The anatomical locations of IHs comprised the head, face, and neck with 67.8%, trunk with 16.1%, and limbs with 16.1%. The morphology of IHs was categorized as a single lesion in 81.7%, multiple lesions in 16.6%, and multifocal lesions in 3.3%.

Complications were observed in 23 cases (12.8%), with the most common complication being ulceration in 22 cases (95.6%). Location of ulcerative

cases including hand and neck in ten cases (45.5%), diaper area in eight cases (36.4%), extremities in three cases (13.6%), and trunk in one case (4.5%). Mean onset of ulceration was two weeks with a range of one to eight weeks. There was one case that showed evidence of visual field defect out of 17 cases examined by the Pediatric ophthalmologist. There was no visceral or hepatic involvement from abdominal ultrasound in all patients who had multifocal lesions (Table 1).

The mean age of the first starting treatment was four months, ranging from one week to 18 months. During follow-up, physicians maintained the same dosage of medication at 2 mg/kg/day, with minor adjustments made based on individual response, ranging from 1.8 to 2.4 mg/kg/day. The mean duration of treatment of propranolol was 13.01±5.33 months on average. Five patients (2.8%) were treated with topical timolol for the residual lesions after discontinuing oral propranolol due to the cutaneous infantile involution (Table 2).

Among patients with ulcerative lesion, 20 patients (90.1%) underwent pulsed dye laser therapy range with one to three sessions, every two weeks combined with oral propranolol. Oral antibiotics were given to 14 patients (63.6%). After two to four weeks of combined propranolol and laser treatment, all lesions were healed.

At the 2-week follow-up, favorable responses were noted in 173 patients (96%), characterized by lightening in color in 172 patients (95.5%), and reduction in size in 146 patients (81.1%). Additionally, 145 patients (80.5%) exhibited both color lightening and size reduction, while 33 patients (18.3%) demonstrated only color lightening and one patient (0.5%) showed only size reduction. Six cases did not respond well to the treatment, including four who had lesions with unchanged size and color, while two developed darker coloration and increased size. Notably, these two patients had a history of irregular medication intake, and upon adherence to regular dosing, improvement was observed (Figure 2).

At the 1-month follow-up appointment, 150 patients (83.3%) attended, with 147 patients (98%) showing favorable treatment responses. By the 6-month follow-up, 141 patients (78.3%) attended the appointment and all of them (100%) exhibited positive treatment responses. At the 1-year follow-up, 128 patients (71.1%) attended the appointment and all of them (100%) showed favorable treatment responses (Table 2).

Table 1. Demographic data of infantile hemangiomas patients

Total (n=180)	n (%)
Sex	
Female	126 (70.0)
Male	54 (30.0)
Type	
Superficial	134 (74.4)
Deep	30 (16.7)
Mixed	16 (8.9)
Locations	
Head and neck	122 (67.8)
Trunk	29 (16.1)
Extremities	29 (16.1)
Number	
Single	147 (81.7)
Multiple	33 (18.3)
Complication	
Ulcerations	22 (12.2)
Diffuse neonatal hemangiomatosis	3 (1.6)
Visual field defect	1 (0.6)

Table 2. Propranolol treatment, outcome and complications (n=180)

Treatment	Value
Age at propranolol initiation (month); mean (range)	4 (0.25 to 18)
Treatments; n (%)	
Oral propranolol	180 (100)
Pulsed dry laser	20 (11.1)
Topical timolol	5 (2.8)
Oral prednisolone	1 (0.6)
Duration of oral propranolol (month); mean±SD	13.01±5.33
Adverse event from oral propranolol; n (%)	2 (1.1)
Hypoglycemia seizure	1 (0.6)
Irritable	1 (0.6)
Treatment response/duration; n (%)	
At 2 weeks (n=180)	173 (96.0)
At 1 month (n=150)	147 (98.0)
At 6 months (n=141)	141 (100)
At 12 months (n=128)	128 (100)

SD=standard deviation

Among the 180 patients treated with oral propranolol, complications were observed in two patients (1.1%). One patient experienced hypoglycemic seizures, and another exhibited irritability and refusal to sleep. The case of hypoglycemia seizure was a 5-month-old infant, she was started on oral propranolol suspension (20 mg per 5 mL) at 1 mg/kg/day and gradually titrated up to 2 mg/kg/day, divided three times daily for over four months. She

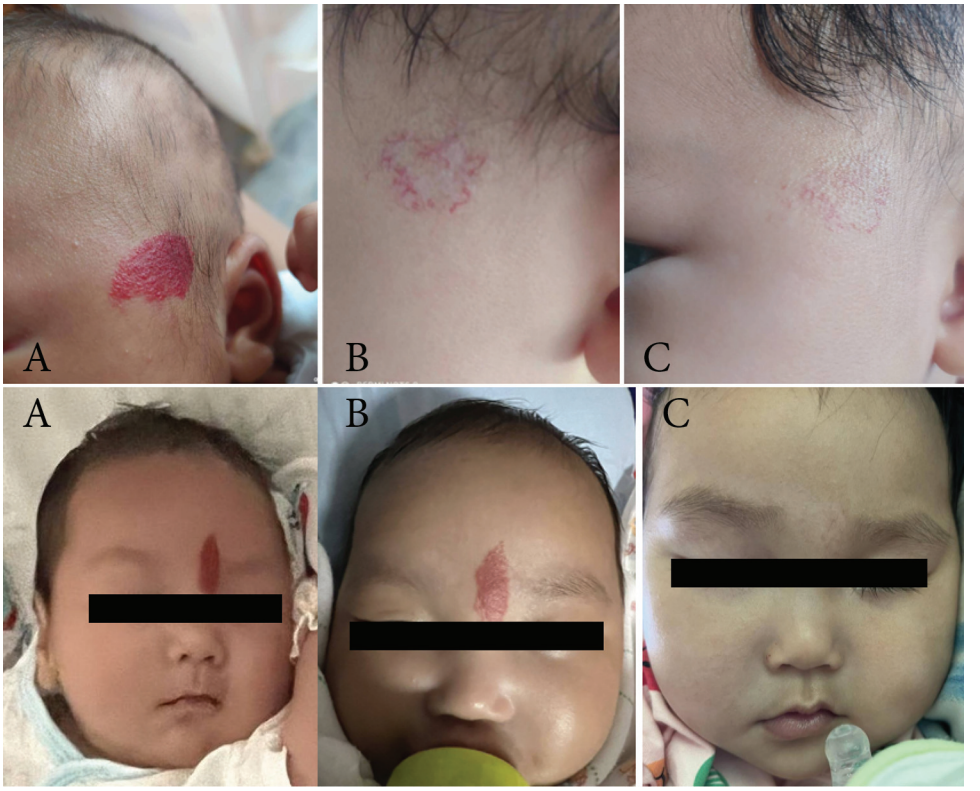

Figure 2. (A) Hemangioma 2-week follow up, (B) Hemangioma 2 months follow up, (C) Hemangioma 6 months follow up.

was taking no other medications and had no history of hypoglycemia. She remained on a dosage of 2 mg/kg/day for three months without adverse effects and with marked improvement in the appearance of her IH. However, on one occasion, following a prolonged period of sleep, her mother administered the routine dosage at 05:00 a.m. Subsequently, she fell asleep and missed her scheduled morning feeding. Approximately 2.5 hours later, at 8:30 a.m., her mother discovered her in a pale and seizure-like state. Upon examination in the emergency room, the attending physician recorded her serum glucose level at 27 mg/dL. Intravenous administration of dextrose was initiated immediately. Subsequently, the medication regimen was temporarily altered to oral prednisolone at a dosage of 2 mg/kg/day. Following the cessation of prednisolone treatment and the resumption of oral propranolol, she did not experience any further episodes of hypoglycemia. In the case of sleep disturbances and irritability, the patient was a 3-month-old female infant. The infant's mother reported improvement in sleep patterns after discontinuation of the medication. As the cutaneous hemangioma regressed, medication was considered for discontinuation.

Discussion

IHs is the most common vascular tumor in pediatric practice, with estimates of incidence varying from 4% to 10% of infants[11,12]. In the present series, seventy percent of the cases were female, which is comparable to other studies in China and USA[2,13].

The majority of the present cases had a single lesion with two-thirds of the cases (67.8%) were on the head, face, and neck. Ulceration was found in 22 cases (12.2%), visual field defect was found in one case. Thus, the treatment is designed to control growth and ulceration, minimize morbidities, preserve function, and minimize psychological and emotional stress from disfigurement.

Ulceration is the most common complication of infantile hemangioma in the present series. There were 22 cases (12.2%), which was comparable to 15.8% in other studies[14] and usually appear in the proliferative phase. Pulsed dye laser was performed in all cases with ulcerative hemangioma, together with standard dose of oral propranolol, with an excellent outcome within one to three sessions of laser treatment (Figure 3).

In the present series, propranolol treatment was initiated at a mean age of four months. Patients

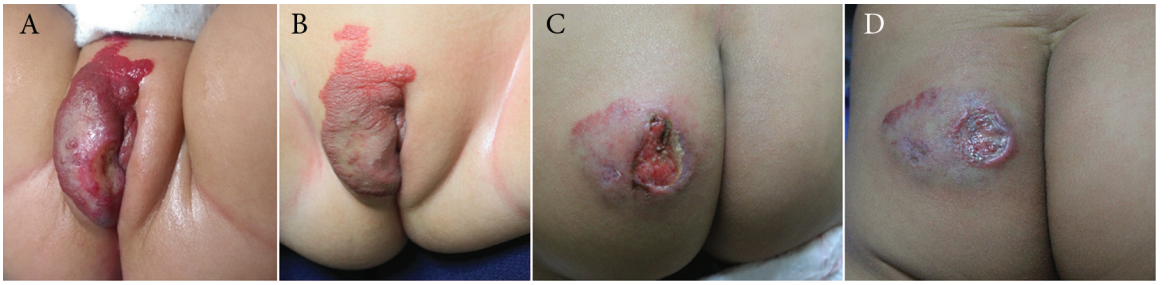

Figure 3. (A) Ulcerative HI at labia before treatment, (B) After 3 sessions of laser treatment and oral propranolol, (C) Ulcerative HI at buttock before treatment, (D) After 2 sessions of laser treatment and oral propranolol.

started oral propranolol as early as one week and as late as 18 months. The present study patients were admitted to initiated propranolol treatment in every case to observe any side effects on the first few doses. All cases used the same dosing regimen and titration protocol, of which the initial dose was 1 mg/kg/day and increased to 2 mg/kg/day within two days.

Propranolol was continued for an average of 13.01±5.33 months. Treatment duration was comparable to the duration of Huang et al.'s study[2]. In studies, the mean response rate was 98%, with a range of 82% to 100%. Twenty-nine studies reported a 100% response rate[15]. As in the present series, they documented a color change within the first 24 hours following initiation of oral propranolol therapy. The authors demonstrated response rates of 96%, 98%, and 100% at two weeks, four weeks, and six months weeks follow up.

Oral propranolol at dose 2 mg/kg/day was noted to be well-tolerated. Very few side effects were reported. Those were agitated sleep[16], irritability, and cool hands or feet[17]. The authors also reported one case out of 180 cases (0.5%) of sleep disturbances and irritability. However serious adverse events including cardiac arrest, severe hyperkalemia, and hypoglycemic coma have also been documented in case reports of 2 mg/kg/day dosing of propranolol for IHs[18-20].

In the 180 cases, there was one case (0.5%) of severe complication. She was a five-month-old healthy baby. After taking propranolol dose of 2 mg/kg/day for four months, she had a life-threatening event in association with severe hypoglycemia and the precipitating factor was prolonged fasting. A literature review of hypoglycemia associated with propranolol therapy in infants and children outside of the neonatal period, in most case, the precipitation was also having a history of poor intake and prolong fasting[9]. Morimoto et al. reported that the incidence of severe hypoglycemia and hypoglycemic convulsions following oral propranolol treatment was estimated to be 0.54% and 0.35%, respectively. Severe hypoglycemia often develops from 05:00 a.m. to 09:00 a.m. and is frequently associated with prolonged periods of fasting, poor feeding, or poor physical conditions[21].

As the mechanism of how hypoglycemia develops in children taking propranolol is not completely understood, glucose homeostasis is thought to be impaired through inhibition of β-adrenergic mediated glycogenolysis, gluconeogenesis, and lipolysis. Children and infants seem to be at higher risk for this adverse effect because their glucose utilization rates are higher in the fasting state, which is as much as 3-fold higher in infants, and attributed partly to their brain mass, which is relatively greater than their body weight[22].

Even though the authors have started all patients on propranolol treatment, they emphasized close observation for the first few doses for complications. They counseled caregivers on how to administer propranolol but warned that even in close observation, serious complication still happens. Therefore, guardians must be informed and deeply concerned not to administer propranolol on empty stomach, in the presence of poor feeding, or in poor physical condition. Furthermore, not to prolong fasting after propranolol administration, and to monitor the child's condition immediately after he or she wakes up[21,23].

What is already known on this topic?

Oral propranolol is currently the first-line therapy for IHs. Studies showed a high efficacy in controlling the growth of IHs. Studies have stated that oral propranolol at standard dose of 2 mg/kg/day has excellent effect and is well tolerated.

What does this study add?

Oral propranolol is effective in treating IH. However, it should be used with caution especially in

children and infants. They are at higher risk of serious adverse effects, including bradycardia, hypotension, bronchospasm, and hypoglycemic coma. Guardians must be informed and deeply concerned not to administer propranolol on an empty stomach, in the presence of poor feeding, or in poor physical condition. Furthermore, not to prolong fasting after propranolol administration, and to monitor the child's condition immediately after he or she wakes up.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical practice guideline for the management of infantile hemangiomas. Pediatrics 2019;143:e20183475.
2. Huang AH, Mannschreck D, Aggarwal P, Mahon M, Cohen BA. Retrospective case series of increased oral propranolol dosage for infantile hemangiomas. Pediatr Dermatol 2020;37:1057-62.
3. Patel NJ, Bauman NM. How should propranolol be initiated for infantile hemangiomas: inpatient versus outpatient? Laryngoscope 2014;124:1279-81.
4. Schneider M, Cremer HJ, Ruef P. A retrospective analysis of systemic propranolol for the treatment of complicated infantile haemangiomas. Acta Paediatr 2014;103:977-83.
5. Moyakine AV, Spillekom-van Koulil S, Küpers EM, van der Vleuten CJM. Influence of infantile hemangioma severity and activity on QoL of patients and their parents: A cross-sectional study. Pediatr Dermatol 2018;35:628-34.
6. Enjolras O, Gelbert F. Superficial hemangiomas: associations and management. Pediatr Dermatol 1997;14:173-9.
7. Love JN, Sikka N. Are 1-2 tablets dangerous? Beta-blocker exposure in toddlers. J Emerg Med 2004;26:309-14.
8. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649-51.
9. Holland KE, Frieden IJ, Frommelt PC, Mancini AJ, Wyatt D, Drolet BA. Hypoglycemia in children taking propranolol for the treatment of infantile hemangioma. Arch Dermatol 2010;146:775-8.
10. Bonifazi E, Acquafredda A, Milano A, Montagna O, Laforgia N. Severe hypoglycemia during successful treatment of diffuse hemangiomatosis with propranolol. Pediatr Dermatol 2010;27:195-6.
11. Hoornweg MJ, Smeulders MJ, Ubbink DT, van der Horst CM. The prevalence and risk factors of infantile haemangiomas: a case-control study in the Dutch population. Paediatr Perinat Epidemiol 2012;26:156-62.
12. Kanada KN, Merin MR, Munden A, Friedlander SF. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. J Pediatr 2012;161:240-5.
13. Luo Y, Zeng Y, Zhou B, Tang J. A retrospective study of propranolol therapy in 635 infants with infantile hemangioma. Pediatr Dermatol 2015;32:151-2.
14. Rodríguez-Ruiz M, Tellado MG, del Pozo Losada J. Combination of pulsed dye laser and propranolol in the treatment of ulcerated infantile haemangioma. An Pediatr (Barc) 2016;84:92-6.
15. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol 2013;30:182-91.
16. Bagazgoitia L, Torrelo A, Gutiérrez JC, Hernández-Martín A, Luna P, Gutiérrez M, et al. Propranolol for infantile hemangiomas. Pediatr Dermatol 2011;28:108-14.
17. Gatts JE, Rush MC, Check JF, Samelak DM, McLean TW. Safety of propranolol for infantile hemangioma in infants less than five weeks corrected age. Pediatr Dermatol 2022;39:389-93.
18. Tosoni A, Cutrone M, Dalle Carbonare M, Pettenazzo A, Perilongo G, Sartori S. Cardiac arrest in a toddler treated with propranolol for infantile Hemangioma: a case report. Ital J Pediatr 2017;43:103. doi: 10.1186/s13052-017-0421-5.
19. Bakalli I, Kola E, Lluka R, Celaj E, Sala D, Gjeta I, et al. Deep coma in a child treated with propranolol for infantile hemangioma. BMC Pediatr 2019;19:216. doi: 10.1186/s12887-019-1598-0.
20. Belen B, Oguz A, Okur A, Dalgic B. A complication to be aware of: hyperkalaemia following propranolol therapy for an infant with intestinal haemangiomatozis. BMJ Case Rep 2014;2014:bcr2014203746. doi: 10.1136/bcr-2014-203746.
21. Morimoto A, Ozeki M, Sasaki S, Baba N, Kuwano Y, Kaneko T. Severe hypoglycemia in propranolol treatment for infantile hemangiomas. Pediatr Int 2022;64:e15278.
22. Cryer PE. Glucose homeostasis and hypoglycemia. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th ed. Philadelphia, PA: Saunders Elsevier; 2008. p. 1503-36.
23. Martin K, Blei F, Chamlin SL, Chiu YE, Frieden IJ, Frommelt PC, et al. Propranolol treatment of infantile hemangiomas: anticipatory guidance for parents and caretakers. Pediatr Dermatol 2013;30:155-9.