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Hemangioma activity score evaluation in infantile hemangioma patients: a retrospective study

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ABSTRACT

Introduction: Infantile hemangioma (IH) is a benign vascular tumor commonly found in children. Generally, no special therapy is required because spontaneous resolutions occur. However, in some cases, therapy is required due to the potential of complications. During therapy, the side effects and effectiveness of therapy must be evaluated. One of the assessment tools is the Hemangioma Activity Score (HAS). HAS is a simple and objective assessment to evaluate the successful treatment of IH by observing swelling, color, and ulceration. The use of HAS in Indonesia is still minimal. This study aims to evaluate HAS before and after therapy in IH patients at Dr. Soetomo General Academic Hospital and Surabaya Skin Centre.

Methods: Twenty-seven patient medical records were selected based on the inclusion and exclusion criteria. This study is an analytic cross-sectional retrospective using consecutive sampling. The collected data were tested for suitability using Cohen's Kappa. Pre- and post-tests were carried out using the Shapiro-Wilk and Wilcoxon tests afterward.

Results: Among 27 IH cases occurred in females (81.4%), with the youngest age of the patient being 1 month and the oldest being 8 years. The onset of lesions in all patients appeared before 1 year of age. The most frequent location for IH lesions was the facial area (51.8%), with a clinical manifestation being plaque (37%). The most common therapy used in this study was pulse dye laser (PDL) (48.1%). Analysis of the difference in HAS before and after therapy showed p value = 0.00, a statistically significant difference in HAS before and after therapy.

Conclusions: The hemangioma activity score is an effective measurement tool for measuring the severity of IH and evaluating the effectiveness of therapy.

Keywords: infantile hemangioma, hemangioma activity score, therapy, human and disease, human and medicine.
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INTRODUCTION

Infantile hemangioma (IH) is the most common vascular tumor in children.[1] In the world, the disease prevalence reaches about 4-5%, while in Indonesia, the prevalence is precisely unknown.[2] From 2008 to 2017, data collected by Pediatrics Division – Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital, Surabaya showed that there were 84 IH cases or about 0.69% of all patients in the Pediatrics Division.[3]

The diagnosis of IH is based on the history and physical examination. The clinical features of the lesion at each phase are essential to diagnose. In IH, there are 2 phases: the proliferative phase, which occurs at the age of 1-3 weeks to the age of 9-12 months, and the involution phase, which occurs at the age of 1-5 years to the age of 7- 8 years. Most cases of IH do not require therapy because spontaneous involution and resolution could occur. However, in some cases, such as complicated IH, therapy could be considered and conducted.[4,5] There are several therapeutic modalities in IH, including pharmacology therapy and non-pharmacology therapy, such as laser and surgery. The successful treatment must be evaluated. This evaluation is one factor that needs to be conducted during therapy for IH patients.[5,6] There are several instruments to evaluate IH therapy. One of them is the Hemangioma Activity Score (HAS). HAS is a scoring system to assess proliferation activity and evaluate therapy's effectiveness. This scoring system is a simple objective assessment and easy to use. HAS evaluates lesions swelling, its color, and ulceration. In addition, HAS could be assessed prospectively from patients or retrospectively from photographs.[7,8] The success evaluation of therapy in IH patients before and after therapy is essential, especially the objective assessments. This evaluation will determine whether the IH lesions improve and whether the therapy given is effective in IH patients.[9] However, until now in Indonesia, no research has evaluated the IH therapy with HAS. Thus, this study aims to evaluate HAS before and after therapy in IH patients at the Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital and

Surabaya Skin Centre for the 2016-2020 period.

MATERIAL AND METHODS

This study is an analytic cross-sectional retrospective using consecutive sampling. Data were obtained from the IH patient's medical records in the Pediatric Division – Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital and Surabaya Skin Centre, from 2016 to 2020. Inclusion criteria were as follows: (1) All patients recorded in the medical record with a diagnosis of IH who were given therapy in the Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital and Surabaya Skin Centre for the 2016-2020 period (2) Patients who had clinical photos before and after therapy in the medical record (3) Patients who had at least 3 visits and treatments. Incomplete medical record data were an exclusion criterion in this study. All patients' profile data (gender, age, lesion onset, location, clinical manifestations, and therapies) were recorded. HAS was evaluated through patients' clinical photographs. The procedure to evaluate HAS was through adding tense swelling and color points. The total number of tense swelling and color points divided by number of items scored was called preliminary HAS. Furthermore, to calculate HAS final score was through adding points of preliminary HAS and ulceration points. HAS was twice conducted before and after therapies by 2 Dermatologist examiners.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) and presented as tables and graphs. All data collected was tested for normality using the Shapiro-Wilk test. Then, the data were subjected to pre and post-tests using the Wilcoxon test. The Wilcoxon test results were said to be statistically significant if $p<0.05$.

RESULTS

This research obtained 104 new IH patients in 2016-2020 at the Dermatology and Venereology outpatient clinic, Dr. Soetomo General Academic Hospital, and Surabaya Skin Center. There were 27 IH patients who met the study inclusion criteria, and 77 patients were excluded because they did not have clinical photos and did not come to follow-up more than 3 times.

Table 1. Profile Data of IH Patients That Meet Inclusion Criteria

Variable	Total (n=27)
Gender, *n (%)*	
Male	5 (18.5)
Female	22 (81.4)
Age, *n (%)*	
Infant (0-11 months)	22 (81.4)
Toddler (12-59 months)	3 (11.1)
Pre-school children (60-72 months)	0 (0)
Children (6-<18 years)	2 (7.4)
Lesion onset, *n (%)*	
Less than 1 year	27 (100)
More than 1 year	0 (0)
Location of the lesions, *n (%)*	
Scalp and retro auricula	3 (11.1)
Face	14 (51.8)
Neck	1 (3.7)
Chest	1 (3.7)
Back	1 (3.7)
Pelvic and genitalia	1 (3.7)
Gluteal	1 (3.7)
Upper extremity	4 (14.8)
Lower extremity	1 (3.7)
Clinical manifestations, *n (%)*	
Macule	1 (3.7)
Plaque	10 (37)
Nodule/tumor	8 (29.6)
Macule + plaque	3 (11.1)
Macule + telangiectasia	3 (11.1)
Plaque + telangiectasia	2 (7.4)
Therapies, *n (%)*	
Topical corticosteroid	1 (3.7)
Oral propranolol	3 (11.1)
PDL	13 (48.1)
Topical corticosteroid + PDL	1 (3.7)
Propranolol + PDL	6 (22.2)
PDL + CO2 laser	1 (3.7)
Topical corticosteroid + propranolol + PDL	1 (3.7)
Topical corticosteroid + PDL + CO2 laser	1 (3.7)

Abbreviations: PDL, pulse dye laser

The profiles of IH patients are described in Table 1. Among 27 patients, namely 22 patients (81.4%) were dominated by females. In comparison, the remaining 5 patients were males (18.5%). Most infant patients (ages 0 - 11 months old) came first for medical check-ups. There were 22 patients (81.4%). All patient lesion onsets in this study (100%) occurred at less than 1 year of age. Most locations for IH were in the face area, with 14 patients (51.8%). Ten patients (37%) had plaque as a clinical manifestation of IH. Pulse dye laser was the most widely used therapy in this study for about 13 patients (48.1%), and the most common combination therapy for IH were propranolol and pulse dye laser, namely 6 patients (22.2%).

This retrospective study showed that 26 out of 27 patients experienced decreased HAS after therapy. This result was due to the patient's duration and type of therapy. Analysis of the difference in HAS of IH patients before and after therapy showed a *p*-value = 0.00, indicating a statistically significant difference in the reduction in HAS before and after therapy. One of the patients who experienced a decrease in HAS is shown in Figure 1. The patient was a 5-month-old female who had IH lesions in the facial area. At the 1st visit, the HAS was 6, with a swelling of 6, which meant

tense swelling was visible, a color of 5, which meant that the lesion was bright red at the beginning of the examination, and 0.5 for ulceration because the patient had ulceration. The patient was given oral propranolol therapy at a dose of 3x1 mg, then increased to 3x3 mg. Also, the patient received PDL therapy 9 times and topical antibiotics for the ulcer area. Treatment was carried out for approximately 9 months. After being given therapy, the HAS was 4, with a swelling of 5, color of 3, and 0 for ulceration because no ulceration was found.

There was another patient who experienced a decrease in HAS was an 8-year-old girl who had residual IH in the form of telangiectasia on the labia majora (shown in Figure 2). This patient received PDL therapy 4 times within 3 months. The parameters used were pulse duration of 10 milliseconds, fluence of 11 J/cm2, spot size of 7 mm, and pulse count of 10. This patient had a significant decrease in HAS from 4 to 0. HAS assessment before therapy from both dermatologists as examiners showed a swelling of 4, which meant there was no swelling at t0 or < 50% reduction at the time of evaluation. A color assessment was obtained of 4, which meant the lesion was bright red at the edge. This patient had no ulceration, so the total HAS at this time before therapy was 4. After treatment, the HAS obtained a total score of 0 for both examiners, showing no swelling during the evaluation. Further, the lesion became skin-colored, and no ulceration was found.

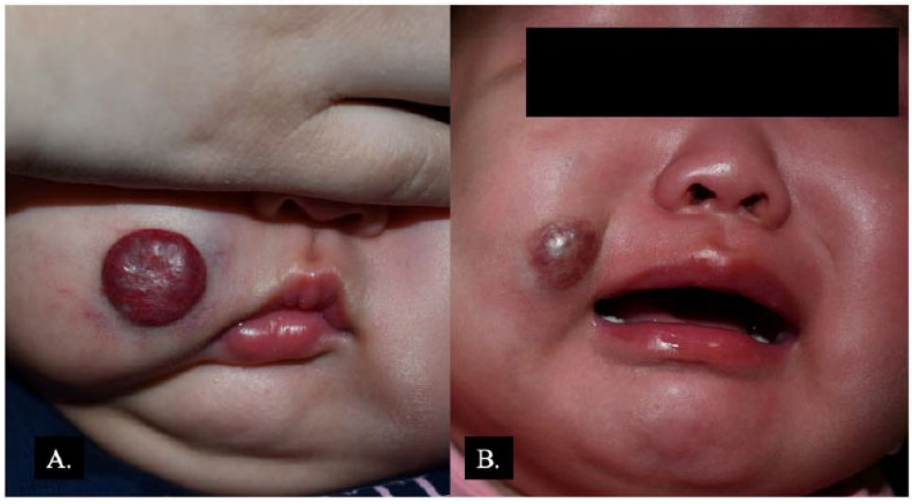

Figure 1. Patient with IH in the facial area after receiving oral propranolol and PDL. **A.** The first time, the patient came with a HAS of 6 **B.** In the 9th month of therapy, clinical improvement of the lesion was identified, and the HAS decreased to 4.

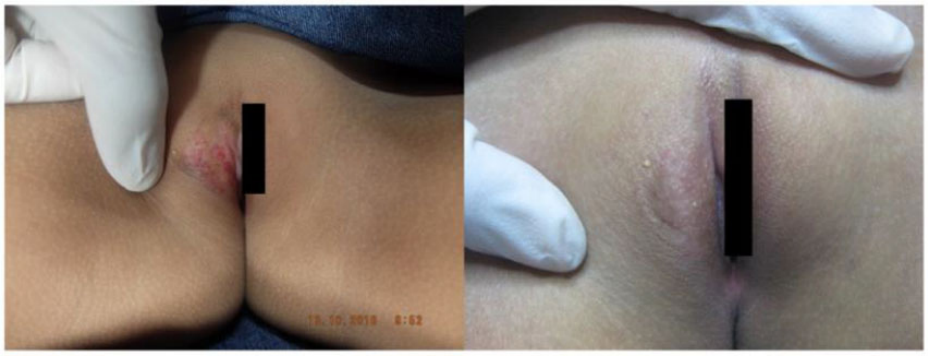

Figure 2. In patients with residual IH lesions in the labia majora area, there were clinical changes and a decrease in HAS from 4 to 0, after PDL therapy.

A suitability test was first carried out using the Cohens Kappa Test of the 27 samples observed, and there was an agreement between the 1st examiner and 2nd examiner in the HAS assessment before and after therapy. In the HAS assessment before therapy, there were 4 samples with low numbers and 23 samples with high numbers. Thus, it could be concluded that the level of agreement between the 1st examiner and 2nd examiner in the HAS assessment before therapy was 100%, with a Kappa co-efficient value of 1,000, with a *p*-value = 0.000. In the HAS assessment after therapy, there were 11 samples with low numbers and 14 with high numbers. There were 2 samples whose assessments did not match those of the 1st and 2nd examiners. Thus, it could be concluded that the level of agreement between the 1st examiner and 2nd examiner in the HAS assessment after therapy was 92%, with a Kappa co-efficient value of 0.851 with a *p*-value = 0.000. Analysis of differences in HAS scores for HI patients before and after therapy at the Dermatology and Venereology Outpatient Clinic, Dr. Soetomo Academic Hospital, and Surabaya Skin Center carried out a pre-post test for 2016-2020. Before that, a sample normality test was carried out. The sample normality test was carried out using the Shapiro-Wilk test. It was concluded that the data in this study was not normally distributed.

Table 2 shows the mean HAS value for IH patients before therapy, which was 4.79 ± 0.69; after therapy, it was 2.81 ± 1.66. Analysis of differences in HAS before and after therapy was carried out using the Wilcoxon test because the study sample was not normally distributed. The Wilcoxon test results obtained a value of *p*=0.00, which indicated that the decrease

Table 2. Analysis Data of IH Before and After Therapy

	Frequency	Minimum	Maximum	Median	Mean ± SD	*p*-value*
HAS before therapy	27	3.0	6.0	4,500	4.79 ± 0.69	*p*=0.000**
HAS after therapy	27	0	5.5	2,250	2.81 ± 1.66	

*Wilcoxon test

**Significant *p*-value <0.05

in HAS after therapy was declared statistically significant.

DISCUSSION

This retrospective study had 27 samples, most of whom were female. It is known that the occurrence of IH was related to the hormone estrogen. This estrogen hormone, synergized with the hormone progesterone, is produced gradually by the placenta from 10 weeks of gestation. A synergetic interaction between estrogen and Vascular Endothelial Growth Factor (VEGF) during IH encouraged the proliferation of outer vascular endothelial cells and the angiogenesis process. This condition was thought to be the reason why IH occurs more often in females than in males.[10]

In this study, age was grouped from infant to children, based on Permenkes number 25, 2014.[11] It was found that 22 (81.4%) of the 27 patients who came for the first time were infants (0-11 months). The age range of IH patients in this study was 1 month to 8 years. Research by Léauté-Labrèze et al. in 2017 also stated the former research that the prevalence of IH was found to be similar in children that were less than 1 year old.[4] IH is a blood vessel tumor that appears in the first year of birth but does not occur at birth. This disease is characterized by rapid postnatal growth followed by a childhood regression period.[5] This reason makes the majority of patients come for treatment at the age before 1 year old.The facial area is the most commonly affected. Other areas are the upper extremity, scalp, and retroauricular regions. This aligns with research conducted by Lydiawati et al. in 2020, which stated that around 60% of IH cases appeared in the craniofacial area, 25% in the body area, and 15% in the extremity areas.[3] However, the exact cause remains unknown. The facial area is one area of the body that receives special attention because it has a psychosocial impact, creates stress, and reduces self-confidence in patients and parents. Therefore, patients and parents would visit the hospital.[12]

The most common IH clinical manifestation found in this study was plaque in 10 patients (37%), and the clinical manifestation of nodules/tumors was found in 8 patients (29.6%). Some patients also had a combination of clinical manifestations, such as macules and plaques, macule and telangiectasia, and plaque and telangiectasia. The clinical manifestation obtained in this research was in accordance with the literature on developing IH lesions. The initial lesion of IH (1st month) is a precursor lesion in the form of a pale area or reddish macula. Further, IH lesions experience a proliferation phase (9-12 months) characterized by the lesion changing into a reddish papule, nodule, or plaque. It continuously experiences an involution phase (>1 year), characterized by the lesion changing to dull red, grayish, or milky white with a flat surface. In this study, the majority of patients came at the age of <1 year, where IH lesions experienced a proliferation phase, namely between the ages of 0-11 months, so that the clinical manifestation that was often found was in the form of macules, plaques, and nodules.[5]

Seventeen patients received single therapy, while 10 received combination therapy. 13 (48.1%) received PDL therapy. The most frequently used combination therapy was a combination of oral propranolol with PDL, which was carried out in 6 patients (22.2%) in this study. Topical antibiotics were given to those who suffered from secondary infections or after laser therapies. The choice of therapy for IH was based on several factors, including size, location of the lesion, psychosocial history, risks, and benefits of therapy because IH lesion's spontaneous involution could occur. However, active intervention, such as pharmacological, surgical, and laser therapy, must be carried out for IH in specific locations and lesions that could cause complications. Until recently, oral propranolol is still the first-line therapy for IH.[5] Wu et al. research in 2019 stated that 36 (70.58%) of 51 IH patients responded well to propranolol, with the recommended dose of 2-3mg/kg/day.[13] Other therapeutic options are systemic and topical corticosteroids. A study on the administration of prednisone to IH patients showed a response rate of 84%, with an average dose of 2.9 mg/kg.[5] Other therapeutic modalities that could be used are lasers, such as PDL, CO2 laser, and Nd: YAG laser.[12,14] Shen et al., in 2015, showed that in China, PDL therapy was an effective modality for reducing the proliferative phase and accelerating the rate of involution and resolution in IH with minimal side effects.[12]

In this retrospective study, a suitability test was conducted to assess HAS before and after therapy. Two dermatologists carried out the suitability test, and significant results were obtained between them, with good strength of agreement. This method was the same as the results of previous research conducted by Janmohamed et al. in 2011 in the Netherlands. HAS was assessed by 3 doctors: a pediatrician, a pediatric surgeon, and a pediatric dermatologist. The result of the suitability test also showed no differences in assessments between raters. The average standard deviation, 3.51 ± 0.87 for 1st rater, 3.39 ± 0.93 for 2nd rater, and 3.48 ± 0.79 for the 3rd rater. The results of the paired t-test analysis obtained a p-value > 0.05 with a strength of agreement of 0.72.[7]

This retrospective study showed that 26 out of 27 patients experienced decreased HAS after therapy. This result was due to the patient's duration and type of therapy. Analysis of the difference in HAS of IH patients before and after therapy showed a p-value = 0.00, indicating a statistically significant difference in the reduction in HAS before and after therapy. The results of this study are similar to those of Herscthal et al. in 2013. The case was a 9-week-old girl with IH in right labia majora. The patient was treated with oral propranolol and pulse dye laser. The IH significantly improved at 6 weeks of size, color, and ulceration treatments. Herscthal et al. also stated that high-risk IH treated with propranolol and pulse dye laser was significantly improved compared to propranolol alone.[15]

There was another patient who received PDL therapy 4 times within 3 months. After treatment, the HAS obtained a total score of 0 for both examiners, showing no swelling during the evaluation. Further, the lesion became skin-colored, and no ulceration was found. This retrospective study is similar to the systematic review and meta-analysis research conducted by Shen et al. in 2015 regarding PDL therapy in IH, which showed that the resolution rate for IH patients given PDL therapy

was 89.1% with a side effect incidence of 6.28%.[12]

The limitations of this retrospective study were the lack of complete medical record data. In addition, standard clinical photographs of patients were minimal, and therapeutic modalities in this study (topical, oral, and laser therapy). Suggestions for further research include conducting a similar study by comparing HAS before and after therapy by applying the same therapy modalities to compare the success rate of therapy.

CONCLUSION

It could be concluded that HAS is an objective assessment for IH patients. It could be used to evaluate the success of therapy. It was found that 26 out of the 27 patients in this study experienced clinical improvement and a significant reduction in HAS after undergoing therapy, topically, orally, and laser or a combination of all therapies.

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this study.

AUTHOR'S CONTRIBUTIONS

Writing analysis and manuscript preparation, PHS; review editing manuscript PHS; guidance in preparing research discussions and analysis, MYL, SS, and BU; All authors also contributed to data analysis and have collectively assumed responsibility for all aspects of this work.

ETHICAL CONSIDERATION

Approval from the institutional ethics committee of Dr. Soetomo General Academic Hospital Surabaya was obtained with protocol number 1092/LOE/301.4.2/X/2022.

REFERENCES

1. Vivcharuk V, Davydenko VY. Influence of age and morphological features on the clinical manifestations and treatment efficacy of hemangiomas in children. Inter Collegas. 2021;8(1), 22-9. doi: https://doi.org/10.35339/ic.8.1.22–29
2. Pope E, Lara-Corrales I, Sibbald C, Liy-Wong C, Kanigsberg N, Drolet B, Ma J. Noninferiority and Safety of Nadolol vs Propranolol in Infants With Infantile Hemangioma: A Randomized Clinical Trial. JAMA Pediatrics. 2022;176(1):34-41. doi: 10.1001/jamapediatrics.2021.4565.
3. Lydiawati E, Zulkarnain I. Infantile Hemangioma: A Retrospective Study. BIKK. 32(1), 21–26. doi: 10.20473/bikk.V32.1.2020.21-26.
4. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet. 2017 Jul 1;390(10089):85-94. doi: 10.1016/S0140-6736(16)00645-0.
5. MacArthur KM, Putthen K. Vascular Tumors. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, editors. Fitzpatrick's Dermatology. McGraw-Hill Education. 2019;2042–71.
6. Dong JY, Ning JX, Li K, Liu C, Wang XX, Li RH, Yue LL, Huang YY, Liu SH. Analysis of factors affecting the therapeutic effect of propranolol for infantile haemangioma of the head and neck. Sci Rep. 2017;7(1):342. doi: 10.1038/s41598-017-00495-z.
7. Janmohamed SR, de Waard-van der Spek FB, Madern GC, de Laat PC, Hop WC, Oranje AP. Scoring the proliferative activity of haemangioma of infancy: the Haemangioma Activity Score (HAS). Clin Exp Dermatol. 2011;36(7):715-23. doi: 10.1111/j.1365-2230.2011.04080.x.
8. Janmohamed SR, van Oosterhout M, de Laat PC, van Rosmalen J, Madern GC, Oranje AP. Scoring the therapeutic effects of oral propranolol for infantile hemangioma: A prospective study comparing the Hemangioma Activity Score (HAS) with the Hemangioma Severity Scale (HSS). J Am Acad Dermatol. 2015;73(2):258-63. doi: 10.1016/j.jaad.2015.05.012.
9. Janmohamed SR, Oranje AP. Scoring systems for infantile hemangioma: the Hemangioma Activity Score versus the Hemangioma Activity and Severity Index. Int J Dermatol. 2016;55(7):e416-7. doi: 10.1111/ijd.13242.
10. Ding Y, Zhang JZ, Yu SR, Xiang F, Kang XJ. Risk factors for infantile hemangioma: a meta-analysis. World J Pediatr. 2020;16(4):377-384. doi: 10.1007/s12519-019-00327-2.
11. Peraturan Menteri Kesehatan Republik Indonesia. Upaya Kesehatan Anak. 2014. Jakarta: Kementrian Keseshatan Republik Indonesia. Available: https://peraturan.bpk.go.id/Home/Details/117562/permenkes-no-25-tahun-2014
12. Shen L, Zhou G, Zhao J, Li P, Xu Q, Dong Y, Zhang Z. Pulsed dye laser therapy for infantile hemangiomas: a systemic review and meta-analysis. QJM. 2015;108(6):473-80. doi: 10.1093/qjmed/hcu206.
13. Wu W, Wang H, Hao J, Gao Z, Li F, Chen Y. Therapeutic efficacy of propranolol for infantile hemangiomas. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;128(2):132-138. doi: 10.1016/j.oooo.2019.04.014.
14. Argentina F, Sibero HT. Management of Infantile Hemangioma'. JUKE Jurnal Kedokteran. 2014;4(7):65-74.
15. Herschthal J, Wulkan A, George M, Waibel J. Additive effect of propranolol and pulsed dye laser for infantile hemangioma. Dermatol Online J. 2013;19(6):18570.