Treatment Modalities and Outcomes of Infantile Hemangiomas at Srinagarind Hospital

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Background: *There are many treatment modalities for infantile hemangiomas. During the past decades, systemic corticosteroid was the mainstay therapy in this condition. However, the most recent option of using oral propranolol has been considered as a first line therapy instead of systemic corticosteroid. On the other hand, there are still many treatment modalities which can be used as an alternative option in treating this condition.*
Objective: *To explore the epidemiology of infantile hemangiomas, treatment modalities and outcomes at Srinagarind Hospital during 2004-2014.*
Material and Method: *Retrospective chart reviewed from the out patient clinic's database at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand.*
Results: *There were a total of 154 infantile hemangiomas. Female to male ratio was 1.8:1. The most common locations of infantile hemangiomas were head and neck areas (69.0%), followed by extremities (21.0%) and trunk (10.0%). Treatment modalities for infantile hemangiomas during the past 10 years (based on initial approaches) were oral propranolol (57.1%), oral prednisolone (17.5%), surgery (10.4%), interferon alpha (9.8%), vincristine (4.5%) and laser (0.6%). All treatment modalities showed high efficacy in treating this condition.*
Conclusion: *There are many effective treatment modalities for infantile hemangiomas. Even though oral propranolol has become the first line therapy in this condition, other treatment options are still effective and useful, especially with those unresponsive to oral propranolol.*

Keywords: *Infantile hemangiomas, Treatment modality, Treatment outcome, Oral propranolol*

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Infantile hemangiomas (IHs) are the most common benign vascular tumors in children[1-3]. The cutaneous manifestations are the findings of erythematous or bluish mass in involved cutaneous areas. Depending on invasion into the skin, there are three types of cutaneous presentations: superficial, subcutaneous (or deep), and mixed. The superficial form (Fig. 1A), represents a red-purplish, smooth, variously lobulated elastic consistency. The deep or subcutaneous hemangioma (Fig. 1B) appears as a well-defined protruding elastic mass, slightly compressible and also covered with normal colored skin, with a faint bluish tint. The mixed type is a combination of both superficial and deep features, characterized by a mixed superficial component and a nodular subcutaneous component (Fig. 1C). The clinical presentations of superficial, deep and mixed type hemangiomas are represented in Fig 1A, 1B and 1C, respectively.

IHs usually appear shortly after birth and manifest as a precursor of vascular patches or pale areas[4]. IHs often proliferate without exceeding their predetermined borders and tend to grow in volume rather than diameter. Once proliferation is completed, the involuting phase usually begins, which is characterized by fading of the initial bright red color and simultaneous softening of the tumor. This is followed by a slow regression that eventually turns out into involuted phase. Afterwards, spontaneous resolution occurs in majority of the IHs cases over a period of time and it is estimated to happen approximately 10% per year. This means around 50% of IHs will be totally involuted by five years, 70% by seven years and 90% by nine years of age[5].

According to the spontaneous involution of

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Fig. 1 Cutaneous presentation of infantile hemangiomas; superficial type (A), deep type (B), mixed type (C).

IHs, most of the cases need only non-intervention therapy. However, some IHs can affect to the adjacent organs or structures depending on locations such as around eyes, nose, mouth, chin, and genitals. Occasionally, IHs may present with some complications such as ulceration and bleeding. Large IHs can also lead to high output heart failure and some in conjunction with other anomalies, especially PHACES[1] syndrome: posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, eye abnormalities, sternal clefting and/or, a supra-umbilicalraphe (Fig. 2).

There were many standard treatments for IHs during the past decades. The most popular one was the use of corticosteroid[7] which was the main stay therapy of this condition. The routes of corticosteroids administration were varied in many forms, including topical corticosteroids, intra-lesion injection[8] and oral formulations. Nevertheless, the most common route was the oral formulation (oral prednisolone) which was usually prescribed to IHs' patients during proliferative phase of growth pattern. The aim of corticosteroids used in IHs was to control growth of hemangioma in proliferative phase. However, some IHs require high-dose, long-term systemic corticosteroids, which in turn is an increased risk for developing hypertension, adrenal cortical insufficiency, immunosuppression, and gastrointestinal bleeding.

Interferon alpha has previously been used with excellent response rates in treating IHs. However, it is no longer recommended due to the high incidence of spastic diplegia[9,10].

The use of vincristine[11] has been described as an alternative treatment in cases which are resistant to corticosteroids. This is thought to act as an antiangiogenic through its effect on the vascular endothelial growth factor. Intravenous vincristine has been shown to have a dramatic effect when combined with systemic corticosteroids and have a low incidence of side effects in children, but it is a vesicant; therefore, extra-vasation must be avoided otherwise skin necrosis may occur.

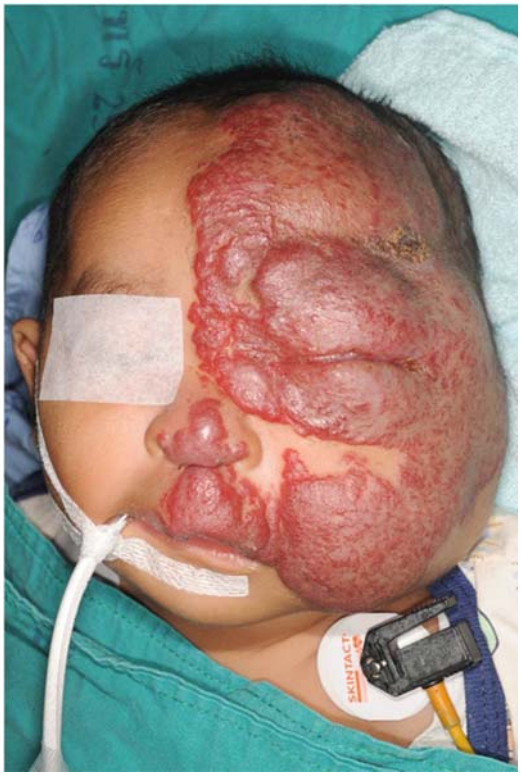

Fig. 2 Large segmental hemangiomas on patient's left face represents cutaneous manifestation of PHACES syndrome.

Pulsed-dye laser[2,3] is an alternative modality with best results achieved during the early proliferative and late regressing phases when the lesion is flattest.

Skin atrophy and pigmentation are the most common adverse effects via this procedure.

Most recently, propranolol described by Leaute-Labreze et al[1] has been considered due to a dramatic effect of this medication on IHs. The authors successfully treated 11 cases and observed a change in the coloration of the hemangioma in all the children as early as 24 hours after initiation of treatment. After the first report in 2008, many studies were set up to explore the efficacy of oral propranolol for treating this condition[3,15,16]. Because of its effectiveness in treating IHs, propranolol is considered as current[17] and first line therapy instead of oral prednisolone. Treating IHs with propranolol is now widely used in many institutions around the world.

Even though oral propranolol has become the first line therapy in IHs, other treatment options are still in use with great results, especially when IHs not responding to oral propranolol. Here we retrospectively recorded the treatment outcomes of IHs via variety of methods of treatments during the past 10 years at Srinagarind Hospital, a tertiary center in northeast of Thailand. This study aimed to represent overall treatment modalities and outcomes of IHs at our institution.

Material and Method

The medical records of the patients whom diagnosed IHs at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand between 2004 and 2014 were retrospectively reviewed. Successful treatment was defined as a more than 50% decrease from baseline in the size and redness of the IHs and a more than 50% increase in the improved function of the involved organs. Statistical analysis was performed using STATA software, version 10. Descriptive statistical methods (mean, standard deviation, median, and frequency) were applied to analyze the demographic data.

The study was approved by the Institutional Review Board No. HE581188.

Results

There were a total of 154 cases diagnosed with IHs at Srinagarind Hospital during the study period and there were 20 cases (16.2%) of premature born infants diagnosed with IHs. Female patients (65.0%) were more common than males (35.0%) with a ratio of 1.8:1. IHs' lesions occurred since birth with documentation of small, preliminary lesions before turning into rapid proliferative growth in all patients (100.0%). The most common locations of IHs were head and neck areas (69.0%). The extremities and trunk were the following locations found in the study by 21.0% and 10.0%, respectively.

There were many specialties involved in taking care of IHs' patients including: pediatricians (74.7%), pediatric surgeons (8.5%), plastic surgeons (5.8%), ophthalmologists (6.5%), otolaryngologist (3.9%) and orthopedists (0.6%). This data were based on the patients' first visit to the clinic.

Treatment modalities

Treatment modalities for IHs during the past 10 years (based on initial approached) were oral propranolol (57.1%), oral prednisolone (17.5%), surgery (10.4%), interferon alpha (9.8%), vincristine (4.5%) and laser (0.6%). Fig. 3 shows the treatment modalities used for treating IHs during the past 10 years in our institution.

Among 154 cases, there were 57 cases (37.0%) diagnosed with IHs during 2004-2008 (Phase I) and the rest 97 cases (63.0%) were recorded between 2009 and 2014 (Phase II).

There were some interesting data in treatment methods during these two periods of time. The majority of cases during Phase I were treated by oral prednisolone (17/57, 29.8%) and surgery (16/57, 28%). While the use of oral propranolol was totally absent during this period of time. Other treatment options were interferon alpha (13/57, 22.8%), intra-lesion corticosteroid injection (7/57, 12.3%), vincristine (3/57, 5.3%) and laser (1/57, 1.8%). Laser treatment was performed as an initial approach only in one case that was diagnosed with PHACES syndrome by plastic surgeons.

Interestingly, Phase II showed a different pattern of treatment modalities. The most common method used was oral propranolol (81/97, 83.5%), followed by oral prednisolone (10/97, 10.3%), vincristine (4/97, 4.1%) and interferon alpha (2/97, 2.1%). There was no case associated with surgery or laser approachas for initial treatment in treating IHs in Phase II. However, with the combination therapy, these two modalities were recorded as the interventions which performed later after other treatments. Fig. 4 shows the treatment tendency of IHs based on their initial approaches.

Treatment outcomes

Each individual treatment modality showed successful treatment outcomes which defined as a more

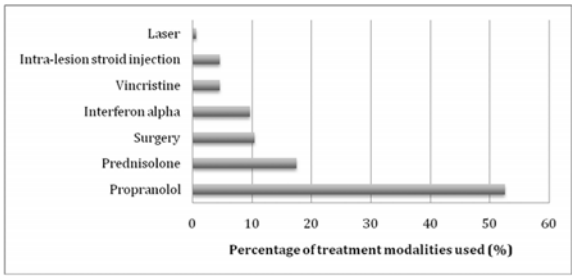

Fig. 3 Treatment modalities used for treating IHs based on initial approach.

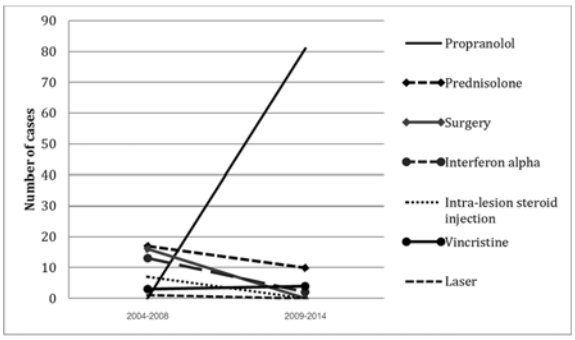

Fig. 4 Treatment tendency of IHs based on their initial approach.

than 50% decrease from baseline in the size and redness of the IHs and a more than 50% increase in the improved function of the involved organs. However, variation of the timing to reach the treatment outcomes as well as the side effects were different among each treatment modality.

Propranolol showed effectiveness in treating IHs. The timing when IHs achieved the treatment response from oral propranolol occurred within two weeks after propranolol administration by 73 out of 81 cases (90.1%) and 100% by two months. There were three evidences of complications which occurred during the study period, two cases of hypoglycemia and one case of hypotension.

Prednisolone also showed effectiveness in treating IHs as well. However, the timing when IHs achieved their treatment response was not clearly documented. Most of the cases continued with oral prednisolone during the proliferative phase of growth pattern. Some serious, documented complications were gastro-intestinal bleedings, hypertension, Cushing appearance, and sepsis.

Interferon alpha indicated a good efficiency in the treatment of IHs in our institution. Timing when IHs achieved their treatment response was not clear. The durations of treatment were varied from one month to nine months. There was an evidence of serum creatinine rising in one patient during the treatment period; therefore, the treatment modality was changed to oral prednisolone.

Intra-lesion corticosteroid injection was documented in seven cases (12.3%) by ophthalmologists. The times of injection were 1-2 times/case. Timing when IHs achieved their treatment response by intra-lesion corticosteroid injection was not clearly documented. No complications were noted according to this treatment modality.

Vincristine was used in seven cases (12.3%) during the past ten years. Timing when IHs achieved their treatment response was not clearly documented. There were evidences of hepatitis in two patients during the treatment period; therefore, the treatment modality was changed to oral prednisolone. Two other patients out of seven had thrombophlebitis due to extravasation and leakage of the drug and caused skin necrosis.

Surgical removal modalities were performed as initial approach in IHs' patients during 2004 and 2008. There were a total of 16 cases (10.4%) that experienced this modality. Varied attempts of surgery were noted which based on the size of the lesions, range from 1-3 times/case. The use of surgery as for the initial approach was absent during Phase II (2009-2014).

Laser treatment (Nd-Yag 532, 1064) was performed as initial approach in 1 case with PHACES syndrome. This modality was performed during proliferative phase of IHs. The treatment outcomes from the laser approach during proliferative phase in this case resulted in some atrophic scars on patient's face. The patient was lost to follow-up and later treated by oral propranolol.

Laser modality by using pulsed-dye laser started to be used in our institution since 2011 by pediatric dermatologists. The use of pulsed-dye laser was performed in involuted phase of IHs rather than in proliferative phase. Cutaneous presentations during this phase of IHs were residual and superficial telangiectasia. The results of IHs treating with pulsed-dye laser in involuted phase were excellent represented by fading of red coloration within 1-2 times of the laser sessions.

Discussion

The data of IHs' patients at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University

showed classic hemangiomas growth pattern by representing as a precursor small pinky, pale patches followed by a rapid growth into proliferative phase. These findings are correlated to all previous studies from our institution by Techasatian el al[1,2] and from other studies[1,2,4] around the world. The epidemiology of IHs showed more frequent in female infants and there were 16.2% of premature infants were recorded in this study. This profile is similar to the general epidemiology of this condition, which usually occurs more common in girls and premature infants. However, the incidence of maternal with history of chorionic villus sampling (CVS) during pregnancy, one of the factors frequently seen in IHs, was not found in this present study. This may be due to the fact that the study type was a retrospective chart review. Some necessary data may not be documented completely.

Treatment of IHs during the past 10 years showed 100% of successful treatment outcomes. However, the response period of IHs to each treatment modality was not well documented. The only data from our retrospective reviewed was the timing when IHs achieved the treatment response from oral propranolol which occurred within two weeks after propranolol administration from 73 out of 81 cases (90.1%). These data are correlated with previous study performed in our institution by Techasatian et al[1] which explored the efficacy of propranolol in treating IHs in the Thai population.

This present study showed a number of specialties involved in management of IHs. According to the diversity of physicians involved, the treatment modalities varied up to their initial visit.

Pediatricians started the treatment by using medication. Two most frequent medications used during the study period were oral propranolol (57.1%) and oral prednisolone (17.5%). Since 2009 when propranolol was initially started to use as a first line and mono-therapy in our institution[3], the incidence of propranolol use were substantially increased which 83.5% usage was reported during 2009-2014. There was no case report using this medication prior during 2009. On the other hand, the percentage of prednisolone use was decreased in the opposite side of propranolol by showing 29.8% of prednisolone use during 2004 and 2008 and 10.3% during 2009 and 2014, respectively. These data represent the fact of powerful effectiveness of propranolol in treating IHs and also reflects the guideline use of propranolol as a first line therapy in IHs' patients[17,19,20].

Pediatric surgeons and plastic surgeons used surgical approached to the IHs' patients. The incidence was 10.4% during the past 10 years. However, this initial approach was absent since 2009. This may due to the fact that the majority of first line therapy was shifted to oral propranolol. Moreover, there was a vascular birthmark clinic setting up in our institution. This clinic included all the sub-specialties involved in taking care of all vascular birthmarks' patients. According to this, the treatment option for every single case was the consensus among the sub-specialties[18].

Ophthalmologists mostly used intra-lesion corticosteroid injection[2] in treating IHs around the eyes. From retrospective record, the data show 100% of improvements after intra-lesion corticosteroid injection. However the response period of IHs to the treatment was not well documented. The incidence of intra-lesion corticosteroid injection for the initial approach was absent after 2009. This may be explained by the same reason of the shifting of treatment modality to oral propranolol.

Interferon alpha was commonly used in pediatric department, especially by oncologists with the percentage of 9.8%. Even though it was an effective modality for IHs, the use of this medication was much less than propranolol and prednisolone during the past ten years. This may be due to the route of drug administration which needs to be injected subcutaneously while propranolol and prednisolone were easily taken by oral route. Moreover, because of the awareness of spastic diplegia which had been reported with this medication[7,8], therefore, the use of interferon alpha was decreased. However, there was no evidence of spastic diplegia by using this medication documented in our institution.

Vincristine is an alternative medication use in IHs[11]. Most of the cases were started the medication due to unfavorable outcome from oral prednisolone or oral propranolol. The most common complication that occurred was the extra-vasation of the drug during intravenous infusion. This also caused thrombophlebitis and skin necrosis on the affected area. Moreover, there were two cases with hepatitis while using this medication and as a result the treatment modality was shifted to oral prednisolone. Even though this is a high effective medication in treating IHs, careful usage and side effects monitoring must be addressed.

Laser modality[12,13] is an alternative treatment for IHs and effective in involuted phase especially with the residual telangiectasia. The most specific laser type for vascular lesion is pulsed-dye laser which started to use in our institution since 2011 by pediatric

dermatologists. The results of IHs treating with pulsed-dye laser in involuted phase were excellent and represented by fading of red coloration within 1-2 times of the laser sessions.

Conclusion

The trend of IHs' treatment was shifting to oral propranolol according to its powerful effectiveness, less side effects and its convenience to use. However, other treatment modalities also showed the efficacy in treating IHs. The data showed 100% in achieving treatment responses in all modalities used in IHs' patients. In the meanwhile, there were various side effects occurred with each individual modality even with oral propranolol. Therefore, the best approach in taking care of IHs' patients is to treat them with specific indications only with those having problematic hemangiomas. Moreover, when any treatment modality is performed, close monitoring should be addressed.

What is already known on this topic?

There are many treatments modalities for infantile hemangiomas during the past decades. Each treatment modality has its own risks and benefits in treating this condition. The treatment option is based on patients' condition and individual physician.

What this study adds?

Tendency of the treatment of infantile hemangiomas is shifting to oral propranolol at Srinagarind Hospital. However, there are still many effective treatments modalities which can be used as an alternative treatment for this condition.

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Potential conflicts of interest

None.

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วิธีการรักษาและผลการรักษาโรคเนื้องอกหลอดเลือดชนิด infantile hemangiomas ในโรงพยาบาลศรีนครินทร์

ลีลาวดี เตชาเสถียร, นพนันท์ ภูคำ

ปัจจุบันมีวิธีในการรักษาโรคเนื้องอกหลอดเลือดชนิด infantile hemangiomas หลากหลายวิธี โดยวิธีการรักษาหลักที่ผ่านมาคือการใช้ยากลุ่มคอร์ติโคสเตียรอยด์ โดยเฉพาะชนิดรับประทาน ซึ่งนับเป็นยาที่ให้ผลการรักษาที่ดีแต่ก็มีผลข้างเคียงจากการรักษาหลายประการ ปัจจุบันมีการเปลี่ยนแนวทางการรักษามาใช้ยาโพรพราโนลอลชนิดรับประทานเป็นยารักษาหลัก ซึ่งให้ผลการรักษาที่ดีและมีประสิทธิภาพสูง ผลข้างเคียงต่ำ อย่างไรก็ตามแนวทางในการรักษาภาวะนี้ยังมีอีกหลาหลายวิธีที่สามารถใช้เป็นทางเลือกในการรักษาได้

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังเก็บข้อมูลจากเวชระเบียนผู้ป่วยที่รักษาที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ระหว่างปี พ.ศ. 2547-2557*

ผลการศึกษา: *มีผู้ป่วยโรคเนื้องอกหลอดเลือดชนิด infantile hemangiomas จำนวน 154 ราย มีสัดส่วนเพศหญิงต่อเพศชาย 1.8:1 ตำแหน่งรอยโรคส่วนใหญ่พบที่บริเวณศีรษะและลำคอคิดเป็นร้อยละ 69 รองลงมาคือบริเวณแขน/ขา ร้อยละ 21 และบริเวณลำตัวร้อยละ 10 วิธีการรักษา infantile hemangiomas ในช่วง 10 ปีที่ผ่านมา ทั้งนี้ประเมินจากวิธีแรกที่ใช้ในการรักษาได้แก่ โพรพราโนลอลชนิดรับประทานร้อยละ 57.1 เพรดนิโซโลนชนิดรับประทานร้อยละ 17.5 การรักษาด้วยการผ่าตัดร้อยละ 10.4 ยา interferon alpha คิดเป็นร้อยละ 9.8 และการรักษาด้วยยา vincristine และการใช้เลเซอร์คิดเป็นร้อยละ 4.5 และ 0.6 ตามลำดับ ทุกวิธีการการรักษาให้ประสิทธิภาพและผลการรักษาที่ดี*

สรุป: *ถึงแม้ว่าในปัจจุบันยาโพรพราโนลอลชนิดรับประทานจะเป็นยาที่ใช้ในการรักษาหลักในการรักษาโรค infantile hemangiomas อย่างไรก็ตามก็ยังมีแนวทางการรักษาอื่น ๆ อีกหลากหลายวิธี ที่สามารถใช้ในการรักษาภาวะนี้และให้ผลการรักษาที่ดีเช่นกัน โดยเฉพาะในกรณีที่รอยโรคไม่ตอบสนองต่อการรักษาด้วยยาโพรพราโนลอล*