RESEARCH PAPER

# Infantile Hemangiomas: Complications and Follow-Up

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**Objective**: To study the risk factors for hemangioma-related complications, treatment indications and analyze the outcome of patients with infantile hemangioma.

**Design**: Retrospective.

**Setting**: University hospital.

**Patients**: Fifty-five patients (1-69 months; median: 12 months) with infantile hemangioma with mean follow-up 19 months. The eligibility was based on the criteria of the International Society for the Study of Vascular Anomalies (ISSVA).

**Intervention**: The surgical treatment included total excision whereas medical treatment was carried out by interferon and /or corticosteroids.

**Main outcome measures**: Data was collected including sex, age, prematurity, age at onset, number, anatomic location and size of hemangioma, age at treatment, cause of treatment decision, family history, presence of extra malformations, involvement of internal organs, presence of life altering or life threatening complications, response to treatment, dose and duration of medications, complications associated with treatment, follow-up period, and final outcome.

**Results**: Thirty-four (62%) patients were followed-up without treatment, whereas 21 others underwent treatment including steroids, interferon, and surgery. The size of hemangioma was a major factor that predicted hemangioma-related complications (*P*=0.002). Patients with hemangioma related complications had bigger lesions (size ≥40cm$^2$ or the longest size on a single plane ≥5 cm). Nineteen patients (34%) had complications, but only 8 (14.5%) out of them had life or function-threatening complications.

**Conclusion**: Although dosing and treatment protocol is still debatable, steroids and interferon are good options for hemangioma treatment. The management strategy should be individualized for each case.

**Key words**: *Complication, Hemangioma, Infants, Outcome, Treatment*.

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Infantile hemangiomas are the most common vascular tumors in children. They usually present as a cutaneous mark at birth in approximately 30% of patients, whereas two thirds of them appear typically around 2 weeks of age. Complete regression is observed by the age of 8 years in the majority [1]. However, a significant subset could be life altering (causing permanent visual loss, disfigurement, and infection due to ulceration), or life threatening (such as obstruction in the airway) [1]. Because of the heterogeneous clinical behavior, infantile hemangiomas require individualized follow up and/or treatment plans. There are many widely used therapeutic options available but no standardized treatment is yet approved [1,2].

We retrospectively analyzed a group of children with infantile hemangiomas to identify the risk factors for developing hemangioma-related complications. Another objective was to describe the characteristics of patients who needed treatment and their treatment indications. We also analyzed the efficacy of different treatment options.

## METHODS

The study included patients who were diagnosed with infantile hemangiomas between January 1996 and January 2009, diagnosed according to the criteria established by the International Society for the Study of Vascular Anomalies (ISSVA) [3]. All patients were evaluated by a pediatric hematology-oncology specialist. The hemangioma size was recorded using "hemispheric" measurements [4]. A soft tape measure was draped over the hemangioma, and the longest diameter and a measurement perpendicular to it were noted, giving a measurement in cm$^2$. The lesions were photographed at baseline and at each follow-up. Whole blood count, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer were evaluated. Ultrasonography/MRI was done for life threatening lesions

(especially in the neck area, causing airway obstruction). All patients underwent an abdominal and transcranial ultrasound (if the fontanel was not closed yet) to identify co-existing congenital malformations, and intra-abdominal or intracranial hemangiomas.

In patients who were thought to be candidates for treatment (either surgical or medical), a second opinion with dermatology, plastic surgery and pediatric surgery consultants was obtained. Patients without complications were evaluated on a two-monthly basis but patients with complications and patients with head and neck lesions were seen more frequently. Patients who had less than three follow up visits were defined as drop out.

The outcome of the lesions was classified as total or marked regression {(*a*) skin change to completely normal, (*b*) telangiectasias in skin, superficial dilated veins, hypopigmentation and/or redundant skin with fibro-fatty residua; and (*c*) shrinkage of the lesion ≥75-50%}, partial regression {shrinkage of the lesion 20-50%}, stable lesion {no change or decrease in size less than 20%} or progression {increase in size in more than 10%}.

All data including sex, age, prematurity, age at onset, number, anatomic location and size of hemangioma, age at treatment, cause of treatment decision, family history, presence of extra malformations, involvement of internal organs, and presence of life-altering or life-threatening complications, response to treatment, dose and duration of medications, complications associated with treatment, follow-up period and final outcome were recorded into a computer database.

*Statistical analysis***:** Statistical analysis was carried out using SPSS 13.0. The data were evaluated using descriptive statistical methods (mean ± standard deviation, median, frequencies and percentages). Chi-square test was used to compare categorical variables and random-effects logistic regression models were used to address potential confounders. The Mann Whitney U-test was used for comparison of independent variables. A two-tailed *P* value less than 0.05 was considered statistically significant.

## RESULTS

The medical records of 55 patients (64% girls) were examined. Eleven (20%) of our patients were born prematurely. The median time for onset of hemangioma was 6 days (range: 6 d-6 wk); the median age at admission was 4 months (range: 1-108 mo).

The patients demographic data and lesions characteristics are shown in ***Table* I**. Three patients had visceral organ involvement {larynx: 1, hepatic: 1, spleen+hepatic: 1 (diffuse neonatal hemangiomatosis)}. Additionally, Dandy-Walker malformation was established in two patients. Our patients did not have PHACE syndrome. Nineteen (34%) patients experienced complications as described in ***Table* I**. Eight patients had more than one complication. Eight (14.5%) patients had life-or function-threatening complications.

We could not show any correlation between gender, location and number of lesions with developing complications. Large lesions (≥5 cm) were 32 times more likely to experience complications than the small lesions (<5 cm) {RR:32.4, (95% CI: 12.2-54.5), *P*=0.002}. Patients with big lesions (≥40 $cm^2$) experienced more complications [RR:14.1 (95% CI: 2.6-75.6), *P*=0.002]. The median size of lesion in patients with complicated hemangiomas was 78±54 $cm^2$ (2-226 $cm^2$), as compared to 15±54 $cm^2$ (3-153$cm^2$) in those without complications (*P*=0.005).

Of the 34 (62%) patients followed-up without treatment, 17 patients had stable lesions at a mean follow

**TABLE I** DEMOGRAPH DATA AND LESION CHARACTERISTICS OF THE PATIENTS (*N*=55)

| | *n (%)* | *Complications, n (%)* |
|---|---|---|
| *Location* | | |
| Head and neck | 33 (60) | 12 (36) |
| Trunk | 8 (15) | 0 |
| Extremities | 5 (9) | 3 (60) |
| Disseminated | 9 (16) | 4 (34) |
| *Number of lesions* | | |
| Single | 31 (56) | 9 (29) |
| 2 or 3 lesions | 12 (22) | 5 (42) |
| Multiple | 12 (22) | 5 (42) |
| *Size (in single plane)* | | |
| <5 cm | 30 (55) | 3 (10) |
| ≥5 cm | 25 (45) | 16 (64)* |
| *Size* | | |
| <40 $cm^2$ | 32 (58) | 5 (16) |
| ≥40 $cm^2$ | 23 (42) | 14 (61)* |
| *Complications* | | |
| Infection | 6 (11) | |
| Ulceration + pain | 7 (13) | |
| Bleeding | 5 (9) | |
| Visual compromise | 4 (7) | |
| Airway obstruction | 3 (5) | |
| High-output heart failure | 2 (4) | |
| Knee disfunction | 1 (2) | |

**P<0.05 for complications.*

up of 19 months (median: 12 months) (***Table* II**). In 21 patients (38%) treatment was initiated (***Table* II**). The indications for therapy were organ dysfunction (8 patients) [visual compromise (3 patients), airway obstruction (1 patient), visual compromise + airway obstruction (1 patient), congestive heart failure (2 patient), knee dysfunction (1 patient)], ulceration (5 patients), disfigurement (5 patients) and rapid growth (3 patients). The median age to start treatment was 3 months (mean: 9 mo, range 1-60 mo). Subclinical (non-overt) disseminated intravascular coagulation (DIC) with high D-Dimer levels was observed in four patients (***Web Table* I**).

Sixteen patients received 2 mg/kg of oral prednisolone given daily as a single morning dose for 4-6 weeks. In patients with life threatening lesions the starting dose was 4 mg/kg/day. The dose was tapered and treatment was stopped between 8-12 weeks. In 5 patients the treatment was switched to IFN because of steroid side effects such as hypertension (2 patients) and cushingoid face (1 patient) and inadequate response despite 6 week full dose steroid treatment (2 patients). Two patients received IFN because of parental refusal for taking steroids. We used IFN in 7 patients at a dose of 3 M IU/$m^2$ three times per week for 6 months. Although a flu-like syndrome occurred in 3 patients, all patients tolerated the treatment well.

Out of the 16 patients receiving steroids, 10 had marked or partial regression. One patient with visual impairment was switched to IFN with excellent outcome. One patient (patient number 6) with a lesion on the eyelid, which was not eligible for upfront total resection, developed amblyopia despite partial regression of the lesion with steroid treatment and underwent surgery to maintain visual capacity.

In two patients with small, well localized lesions in the head and neck area (eyelid, lip and neck), immediate total excision was performed because of cosmetic family concerns. One patient with multiple large hemangiomas in the head and neck area was supposed to be observed without treatment but because of cosmetic concerns the family got a second opinion from a dermatologist who put the child on local steroid, which caused marked regression.

For the ulcerations, local wound care with occlusive dressings were applied. Infected lesions were treated with local and/or systemic antibiotics. Analgesia was achieved with paracetamol orally. Heart failure was managed with inotropic agents

## DISCUSSION

The results of the present study showed that the risk for the infantile hemangiomas-related complications is closely associated with the size of the lesion. The use of corticosteroids was not only useful for the regression of infantile hemangiomas but also served as a bridge therapy for the excision of smaller lesions. The administration of IFN may be a good option in second-line therapy.

There is no controversy regarding the need for treating life-or function-threatening complications such as ocular compromise, respiratory distress, congestive heart failure, gastrointestinal bleeding, or extensive ulceration, which present about 10 to 20 % of the cases [1,2,5-7]. In a prospective study evaluating 1058 patients, 24% had complications (ulceration: 23.2%, visual compromise: 6.9%, airway obstruction: 1.8%, auditory canal obstruction 1.1%, cardiac compromise 0.4%) and 38% received some form of therapeutic intervention [8]. Haggstrom, *et al*. [8] emphasized that morphological subtype, hemangioma size and location were highly associated with complications and need for treatment. In another prospective cohort study evaluating 526 infantile hemangiomas in 433 patients, factors that predicted need for follow-up included ongoing proliferation, larger size, deep component, and segmental and indeterminate morphologic subtypes [9]. Our findings are also similar. The complications are more common in children who are

**TABLE III** THERAPY RESPONSE OF PATIENTS (*N*=55)

| | *n* % | *Therapy response* |
|---|---|---|
| Follow-up without therapy | 34 (62%) | Regression:11 (total:5, partial:6); stable:17; drop out: 6 |
| Only steroid | 10 (18%) | Regresion:9 (marked:7, partial:2); stable:1 |
| Steroid and interferon | 5 (8%) | Regresion:3 (marked:2, partial:1); stable:1; progression:1 |
| Steroid and surgery | 1 (2%) | Total excision: 1 |
| Interferon | 2 (4%) | Regression:2 (marked:1, partial:1) |
| Surgery | 2 (4%) | Total excision: 2 |
| Topical steroid cream | 1 (2%) | Total regression: 1 |

**WHAT IS ALREADY KNOWN?**

- Indication of treatment and standardized treatment for infantile hemangiomas are still debatable.

**WHAT THIS STUDY ADDS?**

- Infantile hemangiomas may be followed without therapy, with treatment required only in complicated cases.
- Steroids remain an effective treatment option, with tolerable side effects.

younger than six months of age and in premature infants [10]. Both groups also showed higher risk in our series.

In many cases, choosing "not to treat" is the best approach [6,8,9]. Systemic glucocorticoids are the mainstay of medical therapy [6,8,9,11-14]. The mechanism of action of corticosteroids is poorly understood. No prospective randomized controlled studies have been performed to search for doses and efficacy. In a study by Boon, *et al.* [15] evaluating 62 patients receiving systemic corticosteroid therapy for problematic infantile hemangiomas; cushingoid facies (71%), personality change (21%), gastric irritation (21%), fungal infection (6%), and reversible myopathy (one patient) were seen as side effects. Diminished longitudinal growth was seen in 35% of the patients and diminished weight gain in 42% of the patients; however, catch-up of growth occurred in most patients. In a study by George, *et al.* [16] 10 out of 22 patients had a systolic blood pressure >105mmHg on at least three occasions during therapy. In our protocol, we preferred using 2 mg/kg prednisone, but in cases with life-threatening complications the dose was raised up to 4 mg/kg/day. Only 3 out of 16 patients had side effects (cushingoid facies:1, hypertension:2), which disappeared after discontinuation of the steroids. In lesions with possible dismal cosmetic result, it is also possible to shrink the size of the lesion with steroids first so that a complete surgical resection with good cosmetic results can be achieved.

IFN is another treatment choice for infantile hemangioma [17,18]. Some studies report favorable results with IFN on a 3-times-a-week schedule [19,20]. However, there is a significant risk of neurotoxicity (spastic diplegia and developmental delay) in 10% to 30% of patients treated with IFN [17-19]. There are some data that relate this neurotoxicity to age, with children less than 12 months having a higher risk. Other side effects of interferon include flu-like syndrome, anemia, neutropenia, thrombocytopenia, changes in liver enzymes, depression, and hypothyroidism [17-19]. We used IFN in seven patients and experienced flu-like syndrome in only 3 patients, which could be managed easily. IFN seems to be an alternative option for treating hemangiomas but taking the cost into account, it still seems to be a second line or salvage treatment. Other treatment modalities of infantile hemangioma are intra-lesional corticosteroid injections, vincristine, beta blockers, laser and surgical therapies [1,20-22].

Although complications are stated to be the most important indication for treatment, in this study, logistic regression showed that the complications did not statistically affect the decision of treatment. The reason for this discordance may be the fact that ten patients received treatment without definitive indications (without life-or function-threatening complications).

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