Infantile Haemangiomas: A Review on Treatment Modalities

Hira Burhan*, Syed Murtaza Hasan Kazmi , Noman Lateef, Abdul Basit Ansari, Mudassir Shah

Dow University of Health Sciences, Karachi

*Corresponding author: Hira Burhan, MD, Dow University of Health Sciences, Karachi, Pakistan; E-mail: hira.burhan91@gmail.com

Received Date: July 11, 2017
Accepted Date: August 07, 2017
Published Date: August 10, 2017

Citation: Burhan, H., et al. Infantile Haemangiomas: A Review on Treatment Modalities. (2017) Int J Hematol Ther 3(3): 1- 5.

Keywords: Hemangiomas; Capillaries; Lasers

Background

Infantile haemangioma is the most common benign vascular tumour-affecting children and are composed of proliferating endothelial tumor cells, and usually manifest as cutaneous birthmarks[1]. They occur 4 times more frequently in females than males, and are especially common among premature births[2]. Approximately half of haemangioma are present at birth; the remainder become evident within the first month of life[3].

The natural course of hemangiomas is divided into: rapid proliferating phase (0 - 1 yr), involuting phase (1 - 5 yr) and the invovluted phase (5 - 10 yr)[4]. Though they can occur in almost all regions of the body, they can be found more commonly in the head and neck (60 %), followed by the trunk (25 %) and then the extremities (15 %). Superficial hemangiomas are located in the papillary dermis, whereas the deep-seated haemangiomas extend deep into the reticular dermis or subcutaneous tissue. Compound haemangiomas exhibit both, superficial and deep characteristics[5].

The most common complication of a haemangioma, occurring in 15 - 25 % of the patients is ulceration. Patients aged between 4 to 6 months are at the highest risk of acquiring this complication[6]. The appearance of gray-white colour on the surface of a haemangioma indicates the development of an ulcer[7]. Ulceration results in scarring along with significant pain and functional impairment, e.g. difficulty moving an affected limb and periocular haemangioma causing astigmatism due to its mass effect on the cornea. Such functional impairment can further lead to amblyopia and a permanent vision loss. Bleeding occurs in 40 % of ulcerations[8]. Another complication is the involvement of vital structures, for example, the liver, can result in high output congestive heart failure[9]. Up to 30 % of patients with large, facial segmental haemangiomas have PHACE (posterior fossa malformations, arterial anomalies, cardiac anomalies, eye abnormalities and sternal/supraumbilical raphe) and the most common extracutaneous findings are arterial anomalies of the cerebral vasculature and coarctation of the aorta[9]. Table 1
### TREATMENT MODALITIES

| WORKING PRINCIPLE | INDICATIONS                           | TYPES                  | USE AND ADVANTAGE                                                                                     | DISADVANTAGES                               |
|-------------------|---------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------|
| LASER THERAPY     | Acts on intravascular Oxyhaemoglobin resulting in Vascular injury | Early or Superficial haemangioma (particularly oral lesions) | -Flash lamp-plumped pulsed laser Used for superficial haemangiomas and promotes regression of involuting haemangiomas Good efficacy | atrophic scars, ulcerations, postoperative purpura and transient hyperpigmentation |
|                   |                                        | -Nd:YAG laser Used for Haemangiomas with subcutaneous component, particularly effective for larger and deep haemangiomas |                                                                  | Painful                                      |
|                   |                                        | -Argon laser Used for vascular birthmarks |                                                                  | Hypertrophic scars                           |
|                   |                                        | -Propanolol and Topical Timolol | First line therapy for proliferative and involutive haemangiomas Preferred for Severe or disfiguring haemangiomas |                                                                  |
|                   | Aim is to reduce morbidity and mortality Mechanism of action depends on the type of drug used | Multiple haemangiomas, rapidly proliferative haemangiomas, and haemangiomas that are affecting vital organs or life threatening | -Oral and intralosional corticosteroids Reserved for propranolol resistant cases Intralesional injection for involuting phase haemangioma with poor response to oral drug or laser therapy | Cushingoid face, disturbance of growth, and susceptibility to serious infections |
|                   |                                        | -IFN-alpha Used for rapidly growing, life-threatening haemangiomas and steroid resistant lesions Short course, reduced financial cost, good tolerance with intralosional use |                                                                  | Influenza-like symptoms, Altered bowel habits, Neutropenia, Aminotransferasemia |
|                   |                                        | -Imiquimod Used for Small and moderate-sized lesions involving the non-conspicuous regions Ease of use, controllability, safety, lack of local irritation. |                                                                  | Risk of haemorrhage and damage to vital structures |
| Surgical Therapy  | Remove or re-contour the residual deformity, scar, hypertrophied tissues, hyperpigmentation, or fibrofatty tissues and to improve cosmetics and function | Proliferative and Involutive haemangiomas | -Used for Non-responsive Proliferating haemangiomason the tip of nose and lip Haemangiomas in the eyelids that impair sight; or occurring on the forehead and scalp Use of naturally expanded skin aiding in primary closure | Laboratory studies can also be useful to assess the possible markers of haemangioma proliferation and differentiation. These include Serum and urinary vascular endothelial growth factor (VEGF), Urinary beta-fibroblast growth factor and Urinary matrix metalloproteinases (MMPs)\[12\]. |

### Diagnosis

Diagnosis is made on the basis of patient history and physical examination. The changes in size and colour of haemangiomas are observed with time, with color changing from bright red to dull purple, and finally in spotted pigment. Deep haemangiomas involving the deep dermis and subcutis, may be skin-colored to blue-violet nodules, depending upon the depth of invasion. It can usually be difficult to distinguish haemangiomas from venous or lymphatic malformations, but accurate diagnosis can be made through a detailed history\[10\].

If diagnosis is still uncertain, a color Doppler ultrasoundography and/or MRI may be used to aid in the diagnosis. Haemangiomas have an isointense or hypointense signal on T1 images and are enhanced on T2 imaging. A rich fibro-fatty infiltration is also demonstrated through high-intensity foci within the involuted tumor on T1 weighted imaging\[11\].

### Treatment

The treatment of IH depends on the following factors: type of haemangioma, stage of the lesion, location and extent, number and distribution of the lesion (segmental/non-segmental), associated systemic involvement, presence or absence of ulceration and psychosocial distress of the parents or child\[1\]. Small isolated or multiple skin lesions on the face found after birth should be treated as soon as possible. Proliferative haemangiomas; however should be treated step by step, including systematic drug therapy followed by laser therapy which is then followed by sclerotherapy. Deep or large haemangiomas can be
managed by drug therapy combined with laser therapy. Involu-
turing or small, stable haemangiomas in non-vital sites require a
close observation. Surgical excision is taken for residual lesions,
scar, hypertrophy, or pigmentation. The growth of the lesions
should be observed, recorded and photographed in the follow-up
period.

Rapidly growing haemangiomas and those associated
with complications like haemorrhage, infection or ulceration
and functional problems, and those involving the facial vital
structures, e.g. eyelids, nose, lips, auricle etc should be treated
immediately[31].

Laser Therapy: Laser therapies treat haemangiomas by acting
on intravascular oxyhaemoglobin, resulting in vascular injury. It
is the recommended for early or superficial haemangiomas and
not suitable for management of deep-seated haemangiomas. The
advantage of laser therapy is the simplicity of use, which can
be repeated at an interval of 2 to 4 weeks[13]. The laser therapy
is particularly effective and safe against the oral lesions, while
minimizing injury to unaffected adjacent tissues and critical
structures, it causes 30 - 95 % lightening in the intraoral port-
wine stains, 90% in the hemangiomas and 70 % in arteriovenous
malformations[14]. There are several types of lasers available
for management of haemangiomas, including argon laser, flash
lamp pumped pulsed dye laser and Nd:YAG laser. The choice
of laser therapy is based on the location, size, and depth of the
lesions. The flash lamp pumped pulsed dye laser in particular has
proven itself as treatment option for superficial haemangiomas,
in numerous studies. In the treatment of haemangiomas with
subcutaneous components, the Nd:YAG laser is the treatment of
choice[32].

Flash lamp-pumped pulsed dye laser destroys the blood
vessels selectively while keeping the overlying skin intact. It is
thus used to promote regression and inhibit endothelial cell pro-
liferation of superficial haemangiomas, and can also accelerate
the regression of involuting hemangiomas[16]. Immediately after
radiation, the treated area turns off-white, with a surrounding
erythematous flare, which resolves after 7 to 14 days. The treated
areas can be smeared with panthenol ointment afterwards. The
patients are followed up at 2 to 4 weeks interval, and a repeated
therapy may be needed after the first session, often at a 4-week inter-
val[17]. FPDL is the first choice for laser treatment of hae-
mangioma with good efficacy and fewer side effects. Common
side effects include atrophic scars, ulcerations, postoperative
purpura and transient hyperpigmentation etc[19].

Nd:YAG laser treatment is very painful and should be
performed under local or general anaesthesia. There is no clear
standard in the operating parameters for continuous Nd:YAG
laser treatment of haemangiomas. Flat lesions are treated with
short exposure time and low energy, while longer exposure time
and higher energy are for thick lesions. One to four days after
therapy, the lesion becomes swollen and will last 5 days. A
blister, or sometimes a scab, may be present, but requires no
incision as the crust of the lesions fall off and the wound heals
within 2 to 4 weeks posttreatment. Treatment can be repeated at
an interval of every 5 to 8 weeks[15]. Compared with argon laser
and FPDL, Nd:YAG laser is more suitable for larger and deep
haemangiomas[30].

The argon laser is used to treat various vascular birth-
marks. It is characterized by an unselective thermal destruction
of blood vessels in contrast to FPDL, resulting in subsequent
damage to the adjacent normal tissues resulting in scarring.
About 40% of infantile haemangiomas may be accompanied by
hypertrophic scars after argon laser treatment, hence limiting its
use in clinical practice and the popularity of the argon laser has
markedly declined over the past decade because of its associated
limitations and the development of the PDL[35]. There are oth-
er laser treatments as well like the potassium titanyl phosphate
(KTP) laser and CO₂ lasers. The KTP laser is often used to treat
large caliber vessels. There is less purpura, swelling, and pain
associated with KTP laser irradiation, but clinical results are
consistently superior with the PDL[33].

Drug Therapy

Drug therapy for infantile haemangiomas aims to re-
base morbidity and mortality and to prevent complications. It is
indicated for multiple haemangiomas, rapidly proliferative hae-
mangiomas, and haemangiomas that are affecting vital organs
or life threatening. Several drugs including corticosteroids, beta
adrenergic blocker, interferons, Imiquimod and etc are used as
drug therapies for haemangiomas[19].

Oral and intraleosional corticosteroids: The mechanism of
action has not been understood completely; however, cortico-
steroids have been shown to inhibit VEGF-A expression and
subsequent proliferation in haemangioma stem cells in a mu-
rine haemangioma model hence slowing down the growth of
proliferative haemangiomas[20]. With the increasing use of pro-
pranolol for problematic haemangiomas, corticosteroids are
only reserved for propranolol resistant cases[19]. The initial oral
dose of prednisone is 4 mg/kg per day for 7 days. If the tumors
stop growing or become smaller, the same dose continues for 3
weeks. Conversely, the dose is increased to 5 mg/kg per day for
7 days, then is tapered down gradually and ceased after 4 to 8
weeks[21]. Intraleosional injection of corticosteroids is used in in-
voluting phase haemangioma patients with poor response to oral
drug therapy or laser therapy. The overall response rate of local
administration is 94.5% with the advantage of fewer side effects
as compared to systemic administration[23].

The main side effects of corticosteroids therapy are the
Cushingoid face, disturbance of growth, and susceptibility to se-
rious infections.

Beta-adrenergic blockers: Beta-blockers, most specifically
propranolol and more recently topical timolol, have been in use
since mid 2008 for infants with severe or disfiguring haemangi-
omas[33]. Propranolol is a nonselective beta-blocker which can
effectively control the proliferation of severe haemangioma and
promote its regression not only during the proliferative phase
but also, to a lesser extent, once growth has been completed. The
possible mechanisms for treatment of infantile haemangiomas
are unclear however some hypothesize that local vasocconstric-
tion may be a factor, which is based on the early color change
and softening of the lesion. One study has demonstrated that
propranolol triggered apoptosis of capillary endothelial cells in
adult rat lung tissue, suggesting a similar mechanism may be
plausible for hemangioma endothelial cells[24]. The most impor-
tant advantages of oral propranolol over glucocorticoids and an-
ti-cancer drugs are efficacy and safety, with fewer side effects
and low cost. The side effects include: transient bradycardia, hy-
potension and gastrointestinal discomfort[23]. Propranolol has replaced corticosteroids as first-line therapy for both proliferative and involutive haemangioma. No protocol for initiating propranolol therapy and the duration of therapy in infants with haemangiomas is universally accepted. Discontinuation of propranolol results in rebound growth in patients. Therefore, many clinicians continue treatment until the growth phase is completed, which can be up to 1 year of age in deep or large infantile haemangiomas[26]. The suggested dosage is 2 mg/kg per day, divided into 2 to 3 doses; up to a duration of 6 - 8 months. Combined low-dose oral propranolol 1.5 mg/kg/day as first-line therapy and oral prednisolone 2 mg/kg/day might be useful in avoiding adverse effects of propranolol in young infants[27].

Interferon alfa inhibits endothelial cell migration and proliferation and specific growth factors (eg, endothelial growth factor, fibroblast growth factor). Interferon-α is used to treat rapidly growing, life-threatening haemangiomas and lesions that are unresponsive to steroids[28]. Due to the potential severe adverse effects, its use is limited to patients with massive or life-threatening haemangiomas. The common complications include influenza-like symptoms, altered bowel habits as well as neutropenia and an increased level of aminotransferases. Although rare, neurotoxicity is remains main concern in the treatment of haemangiomas with interferon[29]. The usual dose of Interferon-α is 3 million U/m² given subcutaneously per day for more than 3 months. The response rate is varied between 80 % and 90 %. If no clinical effect is noticed after 1 month of administration, interferon-α should be discontinued[30]. An intralesional injection of IFN-α is also available, given intratumorally once a day for the first week; then once a week for 7 weeks. The advantages intralesional injection of IFN-α include a short course, reduced financial cost, good tolerance by patients and no major complications[31].

Imiquimod It works via production of a variety of cytokines, including interferon-α, IL-6 and TNF-α. The inhibiting tumor growth and anti-angiogenesis effect of IL-12 may also play an important role in the imiquimod-induced regression of hemangiomas[32]. The efficacy of 5 % imiquimod cream for treatment of infantile haemangiomas has been confirmed by many authors in recent years, especially for small and moderate-sized lesions involving the non-conspicuous regions. It is applied topically once every other day, up to 3 to 5 months. The cream provides advantages in terms of the ease of use, controllability, safety, and lack of local irritation.

Other agents

Anti-cancer drugs (cyclophosphamide and vincristine) have also been used for the treatment of haemangiomas, but high levels of toxicity limits their use. Platelet derived growth factor (PDGF) are often used for ulcerated hemangiomas that are not controlled using steroids or laser therapy[33].

Surgical therapy

With the advent of non-surgical approaches, surgical excision of haemangiomas is no longer the first choice treatment. However, residual deformities after conservative, or laser therapy can be corrected surgically in the involuting phase usually after the age of 3.5 years. The aim of surgery is to remove or re-contour the residual deformity, scar, hypertrophied tissues, hyperpigmentation, or fibrofatty tissues and to improve cosmetics and function. The benefits of excision during late involution include a reduced risk of hemorrhage and a potentially smaller lesion because of the natural course. In addition, because involuted haemangiomas are composed primarily of fibrofatty tissue, complete removal of all tissue is unnecessary, while removing too much tissue could detract from proper contours[34]. Proliferating haemangiomas require surgical excisions if they are located in the tip of nose and lip that do not respond well to other treatments; or haemangiomas in the eyelids that impair sight; haemangiomas occurring on the forehead and scalp, and repeated bleeding from the haemangiomas. Surgical excision of proliferating haemangiomas is potentially hazardous because of the risk of haemorrhage and damage to vital structures associated with them (i.e., head, neck); therefore, only specially trained surgeons should perform this procedure. Certain benefits to early excision include saving a life or preserving vision and decreasing the negative psychosocial effects associated with a cosmetically disfiguring lesion during early childhood. Other benefits of early excision include the use of normally expanded skin to aid in primary closure and the ability to use a relatively avascular tissue plane surrounding actively growing hemangiomas[34].

There is also a latest study which shows that infantile hemangiomas can be successfully treated with coil embolization in combination with corticosteroids, particularly patients with infantile hemangioma associated with Kasabach-Meritttysyndrome (KMS) [35].

Conclusion

Infantile haemangiomas are common, and while most do not require treatment, a small minority do. It is recommended that the physicians should be familiar with the natural history, specific growth characteristics and potential complications associated with infantile haemangioma, including ulceration, risk of disfigurement, functional impairment and potential association with structural anomalies. Educating parents about the variable natural history, prognosis, risks, and benefits of potential treatments and possible complications is also essential.

Conflict of Interests: Authors declare no competing interests.

References

1. Yilmaz, L., Dangoisse, C., Semaille, P. Infantile hemangioma and propranolol: a therapeutic “revolution” Literature review. (2013) Rev Med Brux 34(6): 479-484. PubMed | Crossref | Others
2. Walker, D.M., Hebert, A.A. Topical therapies and medications in the pediatric patient. (2000) Pediatric Clinics 47(4): 867- 876. PubMed | Crossref | Others
3. Finn, M.C., Glowacki, J., Mulliken, J.B. Congenital vascular lesions: clinical application of a new classification. (1983) J Pediatr Surg 18(6): 894-900. PubMed | Crossref | Others
4. Tan, S.T., Velickovic, M., Ruger, B.M., et al. Cellular and extracellular markers of hemangioma, (2000) Plast Reconstr Surg 106(3): 529-538. PubMed | Crossref | Others
5. Zheng, J.W., Zhang, L., Zhou, Q., et al. A practical guide to treatment of infantile hemangiomas of the head and neck. (2013) Int J Clin Exp Med 6(10): 851-860. PubMed | Crossref | Others
6. Chamlin, S.L., Hagstrom, A.N., Drolet, B.A., et al. Multicenter prospective study of ulcerated hemangiomas. (2007) J Pediatr 151(6): 684-689.

7. Shelagh, M., Maguiness, M.D., William, Y., et al. Early White Discoloration of Infantile Hemangioma A Sign of Impending Ulceration. (2010) Arch Dermatol 146(11): 1235-1239.

8. Christison-Lagay, E.R., et al. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. (2007) J Pediatr Surg 42(1): 62-67.

9. Hagstrom, A.N., Garzon, M.C., Baselga, E. Risk for PHACE syndrome in infants with large facial hemangiomas. (2010) Pediatrics 126: e418-426

10. van Rijswijk, C.S., van der Linden, E., van der Woude, H.J., et al. Value of dynamic contrast-enhanced MR imaging in diagnosing and clarifying peripheral vascular malformations. (2002) AJR Am J Roentgenol 178(5): 1181-1187.

11. Baker, L.L., Dillon, W.P., Hieshima, G.B., et al. Hemangiomas and vascular malformations of the head and neck: MR characterization. (1993) AJNR Am J Neuroradiol 14(2): 307-314.

12. Zhang, L., Lin, X., Wang, W., et al. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. (2005) Plast Reconstr Surg 116(1): 200-204.

13. Tanzi, E.L., Lupton, J.R., Alster, T.S. Lasers in dermatology: four decades of progress. (2003) J Am Acad Dermatol 49(1): 1-31.

14. Frigerio, A., Tan, O.T. Laser applications for benign oral lesions. (2015) Lasers Surg Med 47(8): 643-650.

15. Al Buainian, H., Verhaeghe, E., Dierckxsens, L, et al. Early treatment of hemangiomas with lasers. A review. (2003) Dermatology 206(4): 370-373.

16. Stier, M.F., Glick, S.A., Hirsch, R.J. Laser treatment of pediatric vascular lesions: Port wine stains and hemangiomas. (2008) J Am Acad Dermatol 58(2): 261-285.

17. Witman, P.M., Wagner, A.M., Scherer, K., et al. Complications following pulsed dye laser treatment of superficial hemangiomas. (2006) Lasers Surg Med 38(2): 116-123.

18. Ulrich, H., Bäumler, W., Hohenleutner, U., et al. Neodumiyum-YAG Laser for hemangiomas and vascular malformations -- long term results. (2005) J Dtsch Dermatol Ges 3(6): 436-440.

19. Richard, J.A., William, D.J. Infantile Hemangioma Medication. PubMed | Crossref | Others

20. Greenberger, S., Boscolo, E., Adini, I., et al. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. (2010) N Engl J Med 362(11): 1005-1013.

21. Frieden, J.J., Hagstrom, A.N., Drolet, B.A., et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. (2005) Pediatr Dermatol 22(5): 383-406.

22. Chantharatnapiboon, W. Intralesional corticosteroid therapy in hemangiomas: clinical outcome in 160 cases. (2008) J Med Assoc Thai 91(3): 90-96.

23. Pope, E., Chakkittakandiyil, A. Topical timolol gel for infantile hemangiomas: a pilot study. (2010) Arch Dermatol 146(5): 564-565.

24. Sommers, S.S.K., Smith, D.M. Beta blockade induces apoptosis in cultured capillary endothelial cells. (2002) In Vitro Cell Dev Biol Anim 38(5): 298-304.

25. Drolet, B.A., et al. Review Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. (2013) Pediatrics 131(1): 128-140.

26. Bagazgoitia, L., Hernandez-Martin, A., Torrelo, A. Recurrence of infantile hemangiomas treated with propranolol. (2011) Pediad Dermatol 28: 658-662.

27. Koay, A.C., Choo, M.M., Nathan, A.M., et al. Combined low-dose oral propranolol and oral prednisolone as first-line treatment in periorificial infantile hemangiomas. (2011) J Ocul Pharmacol Ther 27(3): 309-311.

28. Ricketts, R.R., Hatley, R.M., Corden, B.J., et al. Interferon-alpha-2a for the treatment of complex hemangiomas of infancy and childhood. (1994) Ann Surg 219(6): 605-612.

29. Dubois, J., Hershon, L., Carmant, L., et al. Toxicity profile of interferon alfa-2b in children: A prospective evaluation. (1999) J Pediatr 135(6): 782-785.

30. Bauman, N.M., Burke, D.K., Smith, R.J. Treatment of massive or life-threatening hemangiomas with recombinant alpha (2a)-interferon. (1997) Otolaryngol Head Neck Surg 117(1): 99-110.

31. Kaselas, C., Tsikopoulos, G., Papouis, G., et al. Intralesional administration of interferon A for the management of severe haemangiomas. (2007) Pediatr Surg Int 23(5): 215-218.

32. Sunamura, M., et al. The antiangiogenesis effect of interleukin 12 during early growth of human pancreatic cancer in SCID mice. (2000) Pancreas 20(3): 227-233.

33. Sugarman, J.L., Mauro, T.M., Frieden, I.J. Treatment of an ulcerated hemangioma: report of a consensus conference. (2013) Pediatr Int 57(4): 738-741.

34. Zheng, J.W., et al. Treatment guideline for hemangiomas and vascular malformations of the head and neck. (2011) J Pediatr surgery 46(5): 691-695.

35. Tetzuka, M., Ohta, M., Ochi, F., et al. Successful treatment by coil embolization for infantile hemangioma with Kasabach-Meritt syndrome of newborn. (2015) Pediatr Int 57(4): 738-741.

36. Gomathy,S., Vamsi, K., Venamandala, et al. The treatment of IH depends on the following factors: Type of hemangioma, stage of the lesion, location and extent, number and distribution of the lesion (segmental/non-segmental), associated systemic involvement, presence or absence of ulceration and psychosocial distress of the parents or child. (2014) J Cutan Aesthet Surg 7(2): 75-85.