INTRODUCTION

Infantile hemangioma (IH) is the most common form of benign vascular tumour of infancy that arises from the abnormal proliferation of endothelial cells and enhanced angiogenesis, with a reported incidence of 4% to 10% ***(Hartzell et al., 2012).***

The incidence is higher (22% to 30%) in extreme low birth weight babies also higher in Caucasian ethnicity, female sex and advanced maternal age, IH is more often found in the face (40%) and neck (20%) regions. For most children with IH, the lesions are small and pose no threat or potential for complication, but in some cases, IHs grow dramatically and destroy tissue, impair function, or even threaten life***(Haggstrom et al., 2007).***

The vascular endothelial growth factor (VEGF) is involved in the proliferating phase of IH. VEGF is the most potent stimulator of hemangioma-derived endothelial cell (HemEC) proliferation and differentiation, and the factor exhibits its pro-proliferative and pro-angiogenic functions by binding to the tyrosine kinase receptor VEGFR-2 on HemECs. Many reports have confirmed that excessive VEGF expression in IH tissue parallels the proliferating phase of IH tissue growth. Conversely, during the involution phase, VEGF expression rapidly decreases, and many inhibitors of angiogenesis are instead expressed ***(Greenberger et al., 2010).***

The treatment options for IH include corticosteroids or surgical excision or, in life- or sight-threatening cases, treatment with vincristine, interferon or cyclophosphamide. Unfortunately, none of these therapeutic modalities is deal due to restrictions or potential serious side effects ***(Chang et al., 2008).***

In 2008, Léauté-Labrèze et al. showed that propranolol has an anti-proliferative effect on severe IHs. After this report, a number of studies further demonstrated that β-blockers other than propranolol were effective at halting hemangioma growth with few adverse side effects. B-blockers are now the preferred treatment for problematic proliferating IHs. To date, it is unknown how β-blockers exert its pharmacologic effect on IHs. The β-ARs, a family of G-protein-coupled receptors that are activated by adrenergic catecholamines, can initiate a series of signaling cascades, thereby leading to multiple cell specific responses. There is evidence suggesting that endogenous catecholamines play a role in basic developmental processes (e.g., embryogenesis and morphogenesis) including the control of cell proliferation, differentiation and migration ***(Anitole-Misleh et al., 2013).***

AIM OF THE WORK

The aim of This study was:

- To study the effect of drug therapy on the level of VEGF in patients with infantile hemangioma after treatment compared to pretreatment level.
- To compare the level VEGF in patients with infantile hemangioma in proliferative and regressive phase.
- To study the relation between VEGF level and clinical response to propranolol therapy.

Chapter One

HEMANGIOMAS AS APART OF VASCULAR ANOMALIES

Definitions and Classifications;

Hemangiomas belong to the group of the vascular lesions. The earliest attempt at classification of vascular anomalies was made by ***Virchow (1863)*** and Wegner (1877), who gave an anatomo-pathologic classification – (a) angioma, (b) lymphangioma ***(Eivazi et al., 2009).***

Later researchers classified the benign vascular anomalies (1) **according to the type of fluid they contained**– (a) hemangioma (blood containing lesion), (b) lymphangioma (lymph-containing lesion), and **(2) According to the size of the vascular channels**– (a) capillary (small diameter vascular channels), (b) cavernous (large diameter vascular channels) ***(Mulliken and Glowacki, 1982).***

In 1982, Mulliken and Glowacki published the biological classification based on the endothelial cell characteristics, physical findings, and natural history of the vascular lesion**.** They divided vascular anomalies into two groups, vascular tumors and vascular malformations**.** Vascular tumors (hemangioma) have endothelial proliferation and vascular malformations show congenital structural abnormalities of vessels but normal endothelial cell turnover ***(Mulliken and Glowacki, 1982)***.

In 1996, this classification was adopted by the International Society for the Study of Vascular Anomalies

(ISSVA) in their first workshop held in Rome the society modified the biological classification in their continuing workshops, and presently ISSVA differentiates vascular tumors from vascular malformations based on their history, clinical appearance, imaging and pathological features, and biological behavior ***(Restrepo et al., 2011).***

Table (1): ISSVA classification of vascular anomalies.

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
Benign vascular tumors	**Simple**	**Combined**	**of major named vessels**	**Associated with other anomalies**
Infantile hemangioma / Hemangioma of infancy Congenital hemangioma Rapidly involuting (RICH) Non-involuting (NICH) Partially involuting (PICH) Tufted angioma Spindle-cell hemangioma Epithelioid hemangioma Pyogenic granuloma (aka lobular capillary hemangioma) **Locally aggressive or borderline vascular tumors** Kaposiform hemangioendothelioma Retiform hemangioendothelioma Papillary intralymphatic angioendothelioma (PILA), Dabska tumor Composite hemangioendothelioma Kaposi sarcoma **Malignant vascular tumors** Angiosarcoma Epithelioid hemangioendothelioma	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations Arteriovenous fistula	capillary-venous malformation capillary-lymphatic malformation capillary-arteriovenous malformation lymphatic-venous malformation capillary-lymphatic-venous malformation capillary-lymphatic-arteriovenous malformation capillary-venous-arteriovenous malformation capillary-lymphatic-venous-arteriovenous m.	**Affect** Lymphatics veins arteries **Anomalies of** origin course number length diameter (aplasia, hypoplasia, stenosis, ectasia / aneurysm) valves communication (AVF) Persistence (of embryonal vessel)	**Klippel-Trenaunay syndrome:** CM + VM +/- LM + limb overgrowth **Parkes Weber syndrome:** CM + AVF + limb overgrowth **Servelle-Martorell syndrome:** limb VM + bone undergrowth **Sturge-Weber syndrome:** facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue overgrowth Limb CM + congenital non-progressive limb hypertrophy **Maffucci syndrome:** VM +/- spindle-cell hemangioma + enchondroma Macrocephaly - CM (M-CM / MCAP) Microcephaly - CM (MICCAP) CLOVES syndrome: LM + VM + CM +/- AVM + lipomatous overgrowth **Proteus syndrome:** CM, VM and/or LM + asymmetrical somatic overgrowth **Bannayan-Riley-Ruvalcaba sd:** AVM + VM +macrocephaly, lipomatous overgrowth

(ISSVA classification for vascular anomalies, May 2014)

Vascular tumors versus vascular malformations

Vascular tumors grow by cellular hyperplasia, but vascular malformations, represent as a localized defect in vascular morphogenesis. Both vascular tumors and malformations may occur anywhere on the body ***(Richter and Friedman, 2012).***

Vascular malformations are the result of abnormal development of vascular elements during embryogenesis and fetal life. These may be single vessel forms (capillary, arterial, lymphatic, or venous) or a combination ***(Al-Adnani et al., 2006)***.

Hemangiomas are the most common benign soft tissue vascular tumor of infancy and childhood ***(Enjolras et al, 2007)***.

Unlike hemangiomas, vascular malformation do not have a growth phase, unless in response to trauma, infections, changes in intravascular pressure, or hormonal changes during pregnancy and puberty. Vascular malformations occur in 1-1.5% of births and have not shown any predisposition to gender or race ***(Redondo, 2007)***.

The actual incidence of vascular malformations may probably be more since many clinicians and diagnostician erroneously report them as hemangioma. vascular malformations are categorized radiologically depending on the dynamics of flow within the vascular channels into slow or low-flow (venous and lymphatic) and fast or high-flow vascular malformations (arterial and arteriovenous) ***(Al-Adnani et al., 2006)***.

Almost all vascular malformations and nearly 40% of hemangiomas eventually require intervention ***(Richter and Friedman, 2012).***

Infantile Hemangiomas (IH) and Congenital Hemangiomas (CH)

ISSVA separates hemangioma into Infantile Hemangiomas (IH) and Congenital Hemangiomas (CH) ***(Enjolras et al., 2012).***

Most common hemangiomas are infantile hemangiomas (IH) 97%, less common are congenital hemangiomas (CH) 3% ***(Pittgen, 2014)***.

IH are not seen at birth although some may have a subtle "precursor "lesion (telangiectasia, pallor, bruise-like, ulcer). Most appear by 1-4 weeks although deeper IH may not be discovered until 2-3 months lifecycle is very specific: Proliferation, Early Involution and Late Involution ***(Kanada et al., 2012)***.

Congenital Hemangiomas are clinically present at birth, full size or minimal postnatal growth, can also be seen prenatally, usually solitary, GLUT-1 negative (unlike HI) and either rapidly involutes during the first year of life or may never show involution. These lesions do not exhibit a proliferative phase and usually do not grow after birth ***(Lee, 2014).***

Rapidly involuting congenital hemangiomas (RICH) are present at birth either as red-purple colour plaques with coarse telangiectasia, as flat violaceous lesions, or as a greyish tumor surrounded by a pale halo with multiple tiny telangiectasia ***(Restrepo et al., 2011).***

RICH undergo a rapid regression phase and completely disappear by 12-18 months of age. Non- involuting congenital

hemangiomas (NICH) are present at birth as pink or purple coloured plaque-like lesions with prominent overlying coarse telangiectasia and peripheral blanching. NICH does not show are gression phase, may grow proportionately with the growth of the child, and can be mistaken for a vascular malformation ***(Restrepo et al., 2011).***

Infantile hemangiomas (IHs)

Epidemiology:

Infantile hemangioma (IH) is the most common tumor of infancy and childhood, occurring in 5% to 10% of infants. About 1 in 20 children bear one type of hemangiomas ***(Kilcline et al., 2008).***

Risk factors accounting for the development of IH have been identified; IH are more common among twins, Caucasians and female infants. Female Infants are suffering from IH three to four folds more than male infants. Premature and low birth weight infants, multiple gestation, advanced maternal age, placental abnormalities are risk factor of Hemangiomas. IH is developed in premature neonates 30% versus 5-10% of all infants ***(Pittgen, 2014).***

Clinical features:

Infantile hemangiomas were not visible at birth and they become obvious as superficial and red color pallor skin lesions during the first days or within the first weeks of life. They are generally noted within the first 2 weeks of postnatal life. However, there is wide variability in this timing. Deep

subcutaneous lesions, such as in the parotid, may not be noted by until the infant is several months old. Their appearance is heralded, in 30% to 50% of infants, by a premonitory cutaneous mark that may resemble a pale spot, telangiectatic or macular red stain, or a bruise-like pseudoecchymotic patch. Infantile hemangioma occur most commonly in the craniofacial region (60%), followed by the trunk (25%) and extremities (15%) ***(Léauté-Labrèze and Taïeb, 2008).***

The delay between birth and the appearance of the vascular tumor is a good diagnostic tool for defining the diagnosis of IH, especially in subcutaneous forms of IH ***(Haggstrom et al., 2006).***

Infantile hemangiomas classification according depth and location

A) Infantile hemangiomas are classified by depth of penetration into three categories: 1. Superficial lesions can be identified as bright red nodule or papule that make white with pressure are often described as "strawberry marks" and appear as a bright red tumor with an irregular surface Account for 50% to 60% of all infantile hemangiomas.

2. Deep lesions in which the color changes are dependent to the depth of the lesions that may be change to blue, purple or no color with pressure. Present as protruding tumors appearing under normal or bluish skin make up approximately 15% of all infantile hemangiomas.

3. Combination of the two superficial and deep haemangiomas lesions. Mixed or combined hemangiomas account for 25% to 35% of infantile hemangiomas ***(Léauté-Labrèze et al., 2011)***

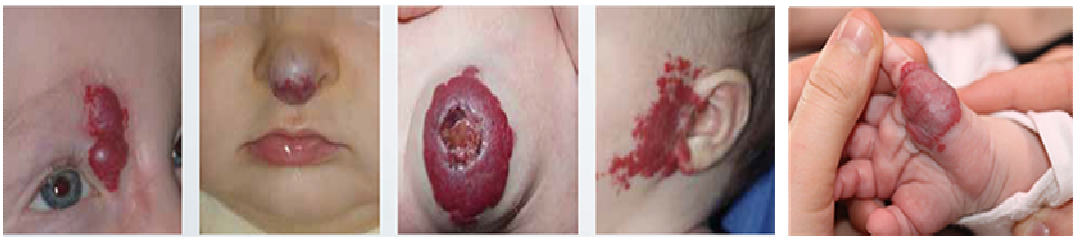

Figure (1): 1-Superficial type2- Mixed type3- Mixed and ulcerated type4- Superficial type5- Nodular type

B) Infantile hemangiomas are also classified by location into; localized, segmental and multifocal. About 77% of haemangiomas are localized (focal), 18% segmental and 5% multifocal ***(Chang et al., 2008).***

Waner et al found that focal hemangiomas were 3 times more common than diffuse or segmental hemangiomas on the face ***(Waner et al., 2003).***

Segmental haemangiomas grow more rapidly than focal type under 6 months ***(Bischoff, 2009).***

The segmental subtype is associated with a higher risk of complications, functional compromise, deformity, and ulceration, as well as a greater need for therapy ***(Haggstrom et al., 2006).***

Patients with segmental hemangiomas of the face should undergo investigation to rule out PHACES syndrome (posterior fossa brain malformations, hemangiomas of the face, arterial

cerebrovascular anomalies, cardiovascular anomalies, eye anomalies, and sternal defects or supraumbilical raphe). Large segmental IH in the anogenital region carry a risk for associated underlying anomalies in the spinal cord, anogenital, and renal anomalies ***(Iacobas et al., 2010)***.

Multiple hemangiomas in a single patient have been called ‘‘disseminated hemangiomatosis.’’ In these infants, the cutaneous lesions are usually tiny (<5 mm in diameter), firm, and dome-like. Any infant with five or more cutaneous tumors should be suspected to harbor visceral hemangiomas (most commonly in the liver, followed by the brain, gastrointestinal tract, and lung) and screened by way of ultrasonography or MRI as indicated ***(Dickie et al., 2009)***.

Although each lesion has its specific growth pattern, most of them have six clinical stages including: 1. Nascent 2. Early proliferative 3. Late proliferative 4. Plateau 5. Involution 6. Abortive ***(Haggstrom et al., 2006).***

Clinical evaluation

Essential components of a first visit with the family of a hemangioma patient include:

1. Establishment of a rapport and open dialog with the parents or care providers.
2. Confirmation of the diagnosis.
3. Photographic documentation.

4. Consideration of the need for pharmacologic or surgical intervention.
5. Determination of the need for other studies to establish the extent of the hemangioma or to rule out associated anomalies.
6. Referral to reputable sources of information and parental support.

Parents with an affected infant, no matter how small or large the hemangioma, are understandably frightened. In general, hemangiomas arise postnatally in previously unblemished infants. Concerns include guilt over possible actions during pregnancy that may have incited this event and frustrations about how other individuals react to the child, as well as other fears of associated anomalies and of further growth of the lesion ***(Jennifer and John, 2005).***

Reassurance is a mainstay, with open discussion of all of these issues. Parents are often afraid to raise these concerns, so a systematic review of hemangioma etiology, misinterpretation by the public, and relationship to other abnormalities is essential. It is helpful for the surgeon to openly recognize that the cause of hemangiomas remains entirely speculative and that there are no known linked factors. Parents should be told explicitly that having an affected child does not predispose them to having other affected children, but that this is a common enough entity that having another child with a hemangioma is not out of the real of possibility ***(Jennifer and John, 2005).***

Photographs are essential—they will provide a basis of reassurance for documented regression at subsequent visits. Many

parents will present with a full set of photos documenting their emotional trial. It may be helpful to sit down and review photographic series of previous patients, documenting the course of regression or surgical results when an operation is indicated. Parents should also be referred to reputable information sources. The internet, an unedited modality, is replete with alarming Web sites, so it is helpful to guide families to respectable authorities. Depending on the level of concern, it may also be helpful to refer new parents to parents of previous patients who have indicated willingness to speak with others the physical examination is generally detailed.

Key questions to consider are:

- Is there dermatomal involvement, affection vision, a bearded involvement, or stridor in the head and neck?
- Is there ulceration?
- Are there multiple cutaneous lesions?
- Is there a lumbosacral or perineal involvement?

(Jennifer and John, 2005)

Developmental phases (Life cycle):

Infantile hemangiomas (IH) are endothelial tumors with aunique biologic behavior—they grow rapidly, regress lowly, and never recur. The three stages in the life cycle of a hemangioma, each characterized by aunique assemblage of biologic markers and processes, are (1) the proliferating phase (0–1 year of age), (2) the involuting phase (1–5 years of age), and (3) the involuted phase (>5 years of age). These stages are typically clinically

apparent and can be distinguished microscopically and immuno-histo-chemically ***(Takahashi et al., 1994).***

In rare cases, proliferating phase may extend until the age of 2 years. During this growth phase, 80% of IH will double their original size, 5% triple and less than 5% will dramatically extend until involving functional, vital or aesthetic prognosis ***(Brandling-Bennett et al., 2008)***.

Histological appearance of hemangioma:

In the proliferating phase, the hemangioma is composed of plump, rapidly dividing endothelial cells that form tightly packed sinusoidal channels. Even at this early stage, the endothelial cells express phenotypic markers of mature endothelium ***(Takahashi et al., 1994)***.

Urinary markers of angiogenesis, such as basic fibroblast growth factor and high molecular weight (MW)matrix metalloproteinases (MMPs) are usually high in infants with proliferating hemangiomas and diminish to normal levels during regression ***(Gonzalez and Reyes, 1991).***

In the involuting phase, there is decreasing endothelial proliferation, increasing apoptosis, and the beginning of fibro fatty replacement of the hemangioma. The net result is loss of volume of the tumor and increasing softness of the overlying skin ***(Lee and Bercovitch, 2013*).**

During the involuted phase, after regression is complete, all that remains are a few tiny capillary-like feeding vessels and